585.00 241 120

#15

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of	Group Art Unit: 1205
GEORGE A. BROOKS	Examiner: R. Henley, III
Serial No. 07/471,287	
Filed: January 26, 1990	PETITION TO REVIVE UNINTENTIONALLY ABANDONED APPLICATION PURSUANT TO M.P.E.P. §711.03(c)
For: METHOD AND COMPOSITION FOR NUTRITIONAL SUPPLEMENTATION DURING EXERCISE AND RECOVERY	2001 Ferry Building San Francisco, CA 94111 (415) 433-4150

Honorable Commissioner of
Patents and Trademarks
Washington, D.C. 20231

Sir:

In response to the Notice of Abandonment mailed November 16, 1992, in the above entitled action for failure to respond to the Official Action mailed April 14, 1992, the applicant hereby petitions pursuant to 37 C.F.R. §1.137(b) to revive the application. The abandonment was unintentional. Applicant responded to the April 14 Official Action and a copy of that response is included with this petition. Apparently, an Advisory Action was sent on October 8, 1992, but applicant's undersigned counsel did not receive it.

Enclosed is the petition fee as set forth in §1.17(m) in the amount of $585.00.

The Commissioner is hereby authorized to charge our Deposit Account No. 12-1420 for any further fees in

CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service as First Class Mail in an envelope addressed to: Commissioner of Patents and Trademarks, Washington, DC 20231 on January 15, 1993

LIMBACH & LIMBACH

Dated: 1/15/93 By Rachel P
Name

070 AA 02/09/93 07471287 1 241 585.00 CK

regard to this patent application. A duplicate copy of this Notice is enclosed for this purpose.

Respectfully submitted,
LIMBACH & LIMBACH

Dated: January 15, 1993 By Michael E. Dergosits
Michael E. Dergosits
Reg. No. 31,243

Atty. Docket No. STIM-01000

Serial No. 07/471,287 & L. File No. STM-1000 By MED:def

In the Matter of the Application of GEORGE A BROOKS

Date Mailed 9-8-92 Due Date 7-14-92

The following has been received in the U.S. Patent Office on the date stamped hereon:

- [x] ~~Oath~~/Declaration of GEORGE A. BROOKS 37 CFR §1.132
- [x] Power of Attorney + EXHIBITS
- [x] Check $175
- [ ] Deposit Account Order Form
- [ ] Drawings _____ sheet(s)
  - [ ] Informal
  - [ ] Formal
- [ ] Assignment
- [x] Letter (transmittal)
- [ ] Information Disclosure (Prior Art) Statement
- [ ] Notice of Appeal
- [x] Extension of Time Request (2 mo) to O.A.
- [x] Amendment/ Response Mailed 4-14-92
- [ ] Affidavit
- [ ] Petition
- [ ] ITU Trademark Application
- [ ] Issue Fee Transmittal Form
- [ ] Trademark Appln. & Specimens
- [ ] Sec. 8 & 15 Affidavits
- [ ] Trademark Renewal Appln.
- [ ] Utility (regular) Appln.
- [ ] Design Patent Appln.
- [ ] Plant Appln.
- [ ] Terminal Disclaimer
- [ ] PCT appln.
- [ ] Small Entity Declaration
- [x] Certificate of Mailing
- [ ] Express Mail Certificate
- [x] Other postcard

n & Limbach
cisco, California

CHECK#: 68955

DATE	REFERENCE/DESCRIPTION	INVOICE AMOUNT	DISCOUNT TAKEN	NET CHECK AMOUNT
08-92	2 MO. EXTENSION STIM-1000	175.00	.00	175.00
	TOTALS ▷	175.00	.00	175.00

DETACH AND RETAIN THIS STATEMENT

Limbach & Limbach
2001 Ferry Building
San Francisco
California 94111

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DATE 09-08-92

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TO THE ER OF COMMISSIONER OF PATENTS AND TRADEMARKS

Robert M

LIMBACH & LIMBACH
2001 Ferry Building
San Francisco, CA 94111
(415) 433-4150

Attorney's Docket No. STIM-01000

In re Application of: George A. Brooks

Serial No.: 07/471,287

Filed: January 26, 1990

For: METHOD AND COMPOSITION FOR NUTRITIONAL SUPPLEMENTATION DURING EXERCISE AND RECOVERY

Honorable Commissioner of Patents
and Trademarks
Washington, D.C. 20231

Sir:

Transmitted herewith is an amendment in the above-identified application.

The fee has been calculated as shown below.

	(Col. 1) CLAIMS REMAINING AFTER AMENDMENT		(Col. 2) HIGHEST NO. PREVIOUSLY PAID FOR	(Col. 3) PRESENT EXTRA	RATE	ADDIT. FEE
TOTAL	* 24	MINUS	** 27	=	X 20=	$0
INDEP.	* 2	MINUS	*** 3	=	X 72=	$0
FIRST PRESENTATION OF MULTIPLE DEP. CLAIM					+220=	$

TOTAL . . . $0

Small Entity 50% Filing Fee Reduction (if applicable) . . . $

*If the entry in Col. 1 is less than the entry in Col. 2, write "0" in Col. 3.
**If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, write "20" in this space.
***If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, write "3" in this space.
The "Highest Number Previously Paid For" (Total or Independent is the highest number found from the equivalent box in Col. 1 of a prior amendment or the number of claims originally filed.)

1. x No additional fee is required.

2. x A check in the amount of $175 is attached (2 month extension/small entity).

3. x Please charge any additional fees, including any fees necessary for extensions of time, or credit overpayment to Deposit Account No. 12-1420.
A duplicate copy of this sheet is enclosed.

4. x Petition for extension of time. The undersigned attorney of record hereby petitions for an extension of time pursuant to 37C.F.R. section 1.136(a), as may be required, to file this response.

CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner of Patents and Trademarks, Washington, D.C. 20231, on September 8, 1992.

Dated: 9-8-92 By: [signature]

Dated: September 8, 1992 [signature]
(Attorney of Record)

Michael E. Dergosits
Registration No. 31,243

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of	Group Art Unit: 1205
GEORGE A. BROOKS	Examiner: R. HENLEY III
Serial No. 07/471,287	REQUEST FOR A TWO MONTH EXTENSION OF TIME TO RESPOND
Filed: January 26, 1990	
For: METHOD AND COMPOSITION FOR NUTRITIONAL SUPPLEMENTATION DURING EXERCISE AND RECOVERY	2001 Ferry Building San Francisco, CA 94111 (415) 433-4150

Honorable Commissioner of Patents
and Trademarks
Washington, D.C. 20231

Sir:

Applicant hereby petitions for a two month extension of time to answer the outstanding Official Action mailed April 14, 1992 regarding the above-referenced patent application. Please find enclosed a check to cover the extension fee.

The Commissioner is hereby authorized to charge payment of any fees associated with this communication or credit any overpayment to Deposit Account No. 12-1420. A duplicate copy of this sheet is enclosed.

Respectfully submitted,

LIMBACH & LIMBACH

Dated: September 8, 1992 By Michael E. Dergosits
Michael E. Dergosits
Reg. No. 31,243
(415) 433-4150

(Atty Docket No. STIM-1000)

CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service as First Class Mail in an envelope addressed to: Commissioner of Patents and Trademarks, Washington, DC 20231 on September 8, 1992

LIMBACH & LIMBACH

Dated: 9-8-92 By Dana E. Jo
Name

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of	Group Art Unit: 1205
GEORGE A. BROOKS	Examiner: R. HENLEY III
Serial No. 07/471,287	
Filed: January 26, 1990	AMENDMENT AND RESPONSE TO OFFICIAL ACTION MAILED APRIL 14, 1992
For: METHOD AND COMPOSITION FOR NUTRITIONAL SUPPLEMENTATION DURING EXERCISE AND RECOVERY	2001 Ferry Building San Francisco, CA 94111 (415) 433-4150

Honorable Commissioner of Patents
and Trademarks
Washington, D.C. 20231

Sir:

Applicant submits the following amendments and remarks in response to the final office action dated April 14, 1992, and respectfully requests reconsideration of the application.

IN THE CLAIMS

Claim 1. (Twice Amended) A method of supplying carbohydrate nutritional supplementation to mammals comprising:

providing an aqueous solution comprising at least one lactic acid salt as a [primary] carbohydrate nutritional component of said solution; and

administering said solution in oral dosage form to a mammalian host in an amount sufficient to beneficially affect the mammal's fluid, electrolyte or carbohydrate balance during exercise and/or subsequent recovery.

CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service as First Class Mail addressed to: Commissioner of Patents and Trademarks, Washington, DC 20231 on September 8, 1992

LIMBACH & LIMBACH

Dated: 9-8-92 By [signature]
Name

Claim 14. (Twice Amended) A carbohydrate nutritional supplement for restoring a mammal's fluid, electrolyte and carbohydrate balance during exercise and subsequent recovery comprising:

an aqueous solution comprising at least one lactic acid salt as a [primary] nutritional component of said solution in an amount sufficient to beneficially affect the mammal's fluid, electrolyte or carbohydrate balance during exercise and/or subsequent recovery, wherein said solution comprises;

a) at least one inorganic lactic acid salt wherein the inorganic lactic acid salts are in a final solution concentration of up to approximately 0.2 weight percent; and

b) at least one organic lactic acid salt, wherein the organic lactic acid salts are in a final solution concentration of from approximately 0.36 to 9.8 weight percent.

In claim 17, on line 1, replace [claim 15] with --claim 14--.

Please cancel Claims 15, 16 and 27.

REMARKS

Claims 1 and 14 were rejected under 35 U.S.C. 112, second paragraph. The phrase "as a primary nutritional component of said solution" was viewed as unclear with respect to whether its limiting effect was qualitative or quantitative.

This rejection is believed avoided in newly amended claims 1 and 14, which no longer state the term "primary". Applicant has instead incorporated functional descriptors -- "carbohydrate" nutrient ...

which is administered in an amount "beneficial" to the exercising athlete.

Claims 1-4, 10-12, 14, 15, 17, 23 and 24 were rejected under 35 U.S.C. 102(b) over the Kober patent. This rejection is respectfully traversed as follows.

As noted in the previous amendment, the mineral salt concentration taught by Kober results in a solution which cannot be used in the manner required by the functional language in the claims. In response to the Examiner's argument that such allegations are not supported by evidence, Applicant provides herein a Declaration under 37 C.F.R. 1.132 by Dr. Brooks, the inventor in the instant application, which specifically addresses this point.

In his remarks, Dr. Brooks demonstrates that the high salt concentrations present in the Kober mineral nutrient supplements is comparable to sea water and illustrates why such solutions would not be beneficial to a person trying to recover from physical exercise. Briefly, Dr. Brooks describes the salt concentrations of physiological fluids as a contrast to Kober's mineral supplements.

In addition, the Examiner's attention is drawn to the above amendment to claim 14 which specifies the solution composition from cancelled claim 16, which was not subject to the § 102 rejection.

In view of Dr. Brooks' declaration and the amendment to the claims which emphasizes the functional characteristics of the lactates in the present invention, applicant respectfully requests that the 35 U.S.C. § 102(b) rejection of Claims 1-4, 10-12, 14, 15, 17, 23 and 24 now be withdrawn.

Claims 1-7, 10-20 and 23-27 were rejected under 35 U.S.C. § 103 over the combination of Millman in

view of Kober. This rejection is respectfully traversed.

It is admitted that Millman does not teach the use of lactate salts in a carbohydrate nutritional supplementation. However, it is argued in the rejection that the art suggests the nutritional composition claimed in this application because Kober teaches addition of lactate salts to improve the stability of such compositions. Applicant notes that the term "stability" may be misleading. Kober prescribes the use of lactate solutions for production of soluble preparations of calcium and magnesium in the presence of phosphates and alkalies, in view of the well known tendency of these substances to form insoluble calcium and magnesium phosphates and hydroxides (page 1, lines 36-50). However, Millman specifically notes that the method provided in his invention results in all of the solid nutrients dissolving rapidly and completely in tap water under ordinary usage conditions. Thus, one skilled in the art would not be led to add the lactate salts of Kober to the Millman solution. The problem Kober solved by addition of lactate (prevention of precipitation), does not exist in the composition taught by Millman which provides easily and rapidly soluble components. Therefore, one skilled in the art would not combine Kober with Millman in the manner suggested by the Examiner. The cited combination of references thus fails as a basis for the § 103 rejection.

Moreover, as discussed in Dr. Brook's Rule 1.132 Declaration, even if one were to add lactate to the solution of Millman, it would not have been obvious that such a solution would be useful as a carbohydrate nutritional supplement to beneficially

affect fluid electrolyte or carbohydrate balance during exercise and/or subsequent recovery. Rather, the evidence supplied with Dr. Brook's declaration clearly demonstrates 50 years of art references teaching away from the use of lactic acid as a nutritional supplement.

Applicant respectfully requests that the 35 U.S.C. § 103 rejection of Claims 1-7, 10-20 and 23-27 based on the Millman/Kober combination now be withdrawn.

Claims 1-27 were rejected under 35 U.S.C. § 103 over the combination of Adibi et al. in view of Kawajiri. This rejection is respectfully traversed as follows.

Applicant has previously argued that the Kawajiri reference is directed to the use of lactic acid for solution stabilization, an entirely differnt result than claimed in the instant invention. Thus, the Adibi and Kawajiri combination would not teach one skilled in the art to use lactate salts as a carbohydrate nutritional component in nutritional suplement for aid in recovery from exercise.

In maintaining this rejection, the Examiner cites In re Lintner as allegedly demonstrating that the addition of a component for a different purpose does not alter a conclusion of the obviousness of a novel composition. Applicant notes that in In re Lintner, the secondary references suggested the use of a sugar with conventional laundry compositions such as that disclosed in the primary reference, and stated:

> "there is no departure from the prior art in terms of the result achieved by the addition of sugar, and the prima facie case of obviousness has not been overcome".

This is clearly a different situation than that of the instant invention, where the addition of lactic acid salts as a nutritional supplement is a clear departure form the prior art.

The court recognized this distinction in In re Lintner, and noted that an obviousness rejection may be rebutted where a claimed composition is shown to possess unexpectedly superior properties or advangages as compared to the prior art compositions. As discussed above, the 37 C.F.R. 1.131 Declaration by Dr. Brooks clearly demonstrates that the beneficial carbohydrate nutritional effects of lactic acid salts in the claimed composition were unexpected in view of the prior art teachings of the negative effects of lactic acid on muscle fatigue.

Thus Applicant respectfully submit that the prima facie case of obviousness is overcome and requests that the 35 U.S.C. § 103 rejection of Claims 1-27 based on the Adibi/Kawajiri combination now be withdrawn.

Applicant believes that the instant amendments and remarks obviate all grounds for rejection of the claims. Reconsideration of the application and its early allowance are respectfully requested.

The Examiner is authorized to contact applicant's undersigned representative by telephone at (415) 433-4150 if, in the opinion of the Examiner,

and interview will in any way expedite the prosecution of this application.

Respectfully submitted,

LIMBACH & LIMBACH

Dated: September 4, 1992

By: Michael E. Dergosits
Michael E. Dergosits
Reg. No. 31,243

2001 Ferry Building
San Francisco, CA 94111
(415) 433-4150

Attorneys for Applicant

Atty. Docket No. STIM-1000

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of	Group Art Unit: 1205
GEORGE A. BROOKS	Examiner: R. HENLEY III
Serial No. 07/471,287	
Filed: January 26, 1990	DECLARATION OF GEORGE A. BROOKS <u>UNDER 37 C.F.R. § 1.132</u>
For: METHOD AND COMPOSITION FOR NUTRITIONAL SUPPLEMENTATION DURING EXERCISE AND RECOVERY	2001 Ferry Building San Francisco, CA 94111 (415) 433-4150

Honorable Commissioner of Patents
and Trademarks
Washington, D.C. 20231

Sir:

I, George A. Brooks, do hereby declare and state that:

1. I am the sole inventor in the above referenced patent application. I have conducted and/or supervised a considerable amount of scientific research in the field of exercise physiology. My curriculum vitae is attached as Exhibit A.

2. I have reviewed the Kober reference which was cited against the claims in the above referenced patent application. The below comments address the teachings of this reference as compared to the invention claimed in the instant application. My below comments also provide a general discussion of the conventional wisdom in the art concerning lactic acid and its effects in exercise physiology.

3. The Kober patent is directed to a food composition that is rich in minerals, and contains lactate as a stabilizing agent. Depending on whether

one follows the wet formulation (lines 24-46) or dry formulation (lines 112-115) of Kober, the resulting solution will have a mineral salt concentration ranging from 11-20%. Such a salt concentration is far too high to benefit fluid, electrolyte or carbohydrate balance during exercise and/or recovery.

4. As provided in Table 12-2 from Eckert, Randall and Augustine, Animal Physiology Mechanisms and Adaptation, Third Edition (Exhibit B), sea water contains 460 and 540 mOsmole of sodium and chloride, respectively. Thus, at 540mM, the NaCL content of sea water would approximate 31 g/l or 3.1%. In effect, the consumption of Kober's mineral salt solution would be worse for the dehydrated athlete than consumption of sea water.

5. For comparison, human plasma concentration is approximately 304 mOsmol, of which 142 mOsmol is from sodium, and 104 mOsmol is from chloride. Because of the relatively high NaCl content of plasma, normal saline for intravenous infusion contains 155 mEq each of Na+ and Cl-, yielding a total NaCl content of 310 mEq (0.9g NaCl per 100ml water, or 0.9%).

6. Thus, Kober's solutions tend to be a full order of magnitude greater in salt concentration than normal saline solutions used for intravenous infusion. In contrast to plasma at 0.9%, the sodium content of sweat is quite small (18 mEq per liter, or 0.05%). The salinity of human plasma rises during exercise because fluids are lost while mineral salts remain in the plasma. For these reasons, salinity of fluid electrolyte replacement beverages typically reflect sweat losses, rather than plasma content. For

example, in the instant application, 0.2% sodium lactate is used to replenish sodium losses during exercise.

7. For many years, the conventional wisdom in the art of exercise physiology was that muscle fatigue was caused by accumulation of lactic acid. Therefore, carbohydrate nutrient compositions having either lactic acid or lactate salts as a nutritional component were not considered beneficial to the exercising athlete because it was believed that additional lactates would accelerate fatigue. Therefore, conventional thought on lactic acid taught away from the use of lactates as a nutritional supplement for exercising athletes. The relevant portions of several textbook references, which date from 1932 to 1986, attached hereto (Exhibit C) demonstrate the conventional wisdom on lactic acid fatique.

8. More recently, beneficial metabolic effects of lactate have been identified. An example of this beneficial effect is reported in the textbook reference attached as Exhibit D. However, even the more recent scientific literature does not disclose or suggest the concept of using lactic acid salts as a carbohydrate nutritional supplemental. This concept was not known prior to the instant invention.

9. I further declare, under penalty of perjury under the laws of the United States of America, that all statements made herein of my own knowledge are true and that these statements were made with the knowledge that willful false statements and the like are punishable by fine or imprisonment, or both,

under Section 1001 of Title 18 of the United States Code.

Dated: 9/4/92

George A. Brooks

7/31/92

Exhibit A

CURRICULUM VITAE

George Austin Brooks
Social Security Number: 055-36-5598
Citizenship: USA

Born: November 25, 1944
Birthplace: New York City
Marital Status: Married; Two Children
Sex: Male

Work Address: Department of Physical Education
103 Harmon Gymnasium
University of California
Berkeley, CA 94720

Work Telephone: (510) 642-2861

Home Address: 2 Lost Valley Court
Orinda, CA 94563

Home Telephone: (510) 376-0826

Present Position: Professor VI; Director, Exercise Physiology Laboratory

Degrees:
B.S., Queens College, CUNY (1966)
M.S., University of Michigan (1968)
Ph.D., University of Michigan (1970)

Athletics:
Captain of the Queens College Track Team (1966)
Collegiate Track Conference Champion, 1000yd. (Indoor, 1966)
Collegiate Track Conference Champion, 880yd (Outdoor, 1966)
Grey Knight Award, for Excellence in Athletics and Scholarship, Queens College (1966)

Dissertation: Temperature, skeletal muscle and liver mitochondrial respiratory functions, and oxygen debt. University of Michigan, 1970.

Dissertation Advisor: Professor John A. Faulkner, Ph.D.
Department of Physiology, University of Michigan, Medical School, Ann Arbor, Michigan

Post Doctoral Research: Muscle Biology Research Laboratory, University of Wisconsin (1971)

Post Doctoral Research Advisor: Professor Robert G. Cassens, Ph.D.

Honors:
Elected Phi Kappa Phi Honor Society (1968)
Elected to Society of Sigma Xi (1971)
Fellow, American College of Sports Medicine (ACSM, 1972)
Member, American Physiological Society (1972)
Member, Research Council AAHPERD (1977)
Member, Board of Trustees ACSM (1981-1984)
Member, Respiratory and Applied Physiology Study Section NIH (1991-1994)

Fields of Interest: Physiological and biochemical effects of exercise, post-exercise oxygen consumption, "oxygen debt," metabolic regulation, lactate glucose and glycogen metabolism, exercise energetics, amino acid metabolism, tracer methodology, adaptation to high altitude, evaluation of human performance.

Editorial Service, Referee Service for the Following Journals:
Journal of Applied Physiology [Editorial Board]
American Journal of Physiology
Medicine and Science in Sport and Exercise [Associate Editor]
Archives of Biochemistry and Biophysics
Research Quarterly for Exercise and Sport
Journal of Gerontology
Proceedings of the Society for Experimental Biology and Medicine
Circulation

Extramural Research Grant Support (Including Direct Cost, Exclusive of Overhead):

Bay Area Heart Research Committee, "Precursors of Glycogen Repletion Following Exercise of Varied Intensities and Durations, " 5/76 - 6/77, $11,189.

Bay Area Heart Research Committee, "Effect of Dietary Manipulation on Cardiac Glycogen Repletion Following Exercises of Varied Intensities," approved for 7/77 for funds were returned when the NIH Grant was received.

National Institutes of Health, DHEW, "Tracer Studies on Lactate Metabolism During Exercise," 4/77 - 3/79, $61,350.

National Institutes of Health, DHEW, "Tracer Studies on Lactate Metabolism During Exercise," 9/79 - 8/82, $119,321.

American Heart Association - California Affiliate, "Amino Acid and Protein Catabolism in Exercise," 7/82 - 6/83, $12,000.

National Institutes of Health, DHEW, "Tracer Studies on Substrate Supply During Exercise," 4/83 - 3/86, $195,650.

American Heart Association - California Affiliate, "Amino Acid and Protein Catabolism in Exercise," 7/83 - 8/84, $20,000.

Office of Naval Research, DOD, "Cold Exposure, Mitochondria and Endurance Training, " (Co-PI with L. Packer), 2/1/83 - 1/31/84, $30,000.

American Heart Association, "Precursors of Cardiac Glycogen Repletion Following Exercise," 7/1/86 - 6/30/89, $99,000.

United States of America Research Foundation, Inc., "Exercise Capacity and Master Formula Supplementation," 11/1/86 - 10/30/87, $25,000.

National Institutes of Health, "Substrate Supply During Exercise," R01 DK 19577, 4/1/90 - 3/30/93, $299,150.

Tobacco-Related Diseases Grant, "Effect of Smoking on Metabolism During Rest and Exercise," 7/1/90-6/30/93, $504,382.

Extramural Research Grant Support (Including Direct Cost, Exclusive of Overhead) continued:

National Institutes of Health, "Developmental Aspects of Iron Nutrition," (Subcontract) R37 DK1387, 7/1//91 - 4/30/92, $112,514.

National Institutes of Health, "Developmental Aspects of Iron Nutrition," DK1387, 5/1/92 - 4/30/97, $1,120,807 (direct costs) [Pending].

Teaching Grant Support:

Regents Undergraduate Improvement Instruction Grant, "Videotaped Demonstration of Laboratory Experiments in Exercise Physiology," Academic 1975-1976.

Academic Senate Mini-Grant, "Illustrated Lectures in Exercise Physiology," Academic 1975-1976.

TIES Mini-Grant for Teaching Improvement, "Illustrated Lectures in Exercise Physiology, PE 105B," Academic 1975-1976.

University Grant for Teaching Improvement, "Teaching and Research in Physical Education and Kinesiology," Academic 1976-1977.

Regents Instructional Improvement Grants, Academic 1990-1991.

Teaching:

Nominated University of California Distinguished Teaching Award, 1983, 1984.

Departmental Service:

Undergraduate Advisor

Graduate Advisor

Chairman's Advisory Committee

Academic Programs Committee

University Service:

Acting Departmental Chairman, 6/77 to 9/78, 6/79 to 3/80, 1/85 to 7/85.

Assistant Dean, College of Letters and Science, 3/83 to 12/84

Member, Senate Committee on Courses of Instruction, 9/91- Present

Service to Scholarly Societies:

Member: Administrative Council Southwest Chapter American College of Sports Medicine

Member: National Institutes of Health, Respiratory and Applied Physiology Study Section

Elected: President of Southwest Chapter American College of Sports Medicine

Elected: Vice-President, American College of Sports Medicine

Community Service:

Manager, El Cerrito Lions Baseball Team (6-8 yr) 1985-1987
Coach, El Cerrito Earthquakes Soccer Team (7-10 yr) 1985-1987
Member, Board of Directors El Cerrito Youth Baseball League 1986-1987
FIFA Certified Soccer Referee, Alameda-Contra Costa Soccer League 1986-1987
Coach, Bearcats Baseball Team, Orinda Youth Organization (10-12 yr) 1988, 1989
Coach, Blues Soccer Team, Orinda Youth Organization (10-12 yr) 1988
Manager, Bearcats Baseball Team, Orinda Youth Organization (Boys 10-12 yr) 1990
Manager, Bearcats Baseball Team, Orinda Youth Organization (Boys 13-15 yr) 1991
Division Director, Orinda Youth Organization (Boys 13-15 yr) 1991, 1992
Head of Baseball, Orinda Youth Organization 1992.

Books Published by G.A. Brooks:

Brooks, G.A. (Ed.) Perspective on the Academic Discipline of Physical Education, Human Kinetics Publishers, Champaign, IL, 1981.

Brooks, G.A. and T.D. Fahey. Exercise Physiology: Human Bioenergetics and Their Application, John Wiley and Sons, New York, 1984.

Brooks, G.A. and T.D. Fahey. Fundamentals of Human Performance, Macmillan Publishing Co., New York, 1986.

Peer Reviewed and Invited Publications of G.A. Brooks:

1. Welch, H.G., J.A. Faulkner, J.K. Barclay and G.A. Brooks. Ventilatory response during recovery from muscular work and its relations with O_2 debt. Med. Sci. Sports 2:15-19, 1970.

2. Brooks, G.A., K.J. Hittelman and R.E. Beyer. Temperature, skeletal mitochondrial respiratory functions and oxygen debt. Am. J. Physiol. 220:1053-1059, 1971.

3. Brooks, G.A., K.J. Hittelman, J.A. Faulkner and R.E. Beyer. Temperature, liver mitochondrial respiratory functions, and oxygen debt. Med. Sci. Sports 2:72-74, 1971.

4. Brooks, G.A., K.J. Hittelman, J.A. Faulkner and R.E. Beyer. Tissue temperatures and whole-animal oxygen consumption after exercise. Am. J. Physiol. 221:427-431, 1971.

5. Mylrea, K., G.A. Brooks and R.G. Cassens. Glycogen synthesis and the metabolism of lactic acid after exercise. Am. J. Physiol. 32:439-441, 1972.

6. Brooks, G.A., K.E. Brauner and R.G. Cassens. Glycogen synthesis and the metabolism of lactic acid after exercise. Am. J. Physiol. 224:1162-1166, 1973.

7. Brooks, G.A. Changing requirements for the Ph.D. in physical education with a specialization in exercise physiology. In: Issues in Physical Education, G.H. McGlynn (Ed.), National Press, Palo Alto, 1973.

8. Brooks, G.A. and R.G. Cassens. Respiratory functions of mitochondria isolated from stress-susceptible and stress resistant pigs. J. Animal Sci. 37:668, 1973.

9. Claremont, A.D. and G.A. Brooks. An improved method of quadriceps thermocouple implantation. Eur. J. Appl. Physiol. 32:183-186, 1974.

10. Brooks, G.A., M.J. Bissell and J.A. Bassham. Desalting of animal tissue extracts sample *in vivo* for separation by two dimensional chromatography. Chemical Biodynamics Quarterly 113-116, August, 1974.

11. Gaesser, G.A. and G.A. Brooks. Muscular efficiency during steady-rate exercise: Effects of speed and work rate. J. Appl. Physiol. 38:1132-1139, 1975.

12. Claremont, A.D., F. Nagle, W.D. Reddan and G.A. Brooks. Comparison of metabolic temperature heart rate and ventilatory responses to exercise at extreme ambient temperatures (0° and 35° C). Med. Sci. Sport 7:150-154, 1975.

13. Musch, T.I. and G.A. Brooks. Effect of diet and metabolic rate on open circuit calculations of VO_2 and VCO_2. Research Quarterly 47:731-740, 1976.

14. Donovan, C.M. and G.A. Brooks. Muscular efficiency during steady-rate exercise II: Effects of walking speed and work rate. J. Appl. Physiol. 43:431-439, 1977.

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Exhibit B

THIRD EDITION

ANIMAL PHYSIOLOGY

MECHANISMS AND ADAPTATIONS

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TABLE 12-2 Composition of extracellular fluids of representative animals (concentrations in millimoles per liter of H_2O).

	Habitat*	Milliosmoles	$[Na^+]$	$[K^+]$	$[Ca^{2+}]$	$[Mg^{2+}]$	$[Cl^-]$	$[SO_4^{2-}]$	$[HPO_4^{2-}]$	Urea
Seawater†		1000	460	10	10	53	540	27		
Coelenterata										
Aurelia (jellyfish)	SW		454	10.2	9.7	51.0	554	14.6		
Echinodermata										
Asterias (starfish)	SW		428	9.5	11.7	49.2	487	26.7		
Annelida										
Arenicola (lugworm)	SW		459	10.1	10.0	52.4	537	24.4		
Lumbricus (earthworm)	Ter.		76	4.0	2.9		43			
Mollusca										
Aplysia (sea slug)	SW		492	9.7	13.3	49	543	28.2		
Loligo (squid)	SW		419	20.6	11.3	51.6	522	6.9		
Anodonta (clam)	FW		15.6	0.49	8.4	0.19	11.7	0.73		
Crustacea										
Cambarus (crayfish)	FW		146	3.9	8.1	4.3	139			
Homarus (lobster)	SW		472	10.0	15.6	6.7	470			
Insecta										
Locusta	Ter.		60	12	17	25				
Periplaneta (cockroach)	Ter.		161	7.9	4.0	5.6	144			
Cyclostomata										
Eptatretus (hagfish)	SW	1002	554	6.8	8.8	23.4	532	1.7	2.1	3
Lampetra (lamprey)	FW	246	120	3.2	1.9	2.1	96	2.7		0.4
Chondrichthyes										
Dogfish shark	SW	1075	269	4.3	3.2	1.1	258	1	1.1	376
Carcharhinus	FW		200	8	3	2	180	0.5	4.0	132
Coelacantha										355
Latimeria	SW		181	51.3	6.9	28.7	199			
Teleostei										
Paralichthys (flounder)	SW	337	180	4	3	1	160	0.2		
Carassius (goldfish)	FW	293	142	2	6	3	107			
Amphibia										2
Rana esculenta (frog)	FW	210	92	3	2.3	1.6	70			40
Rana cancrivora	FW	290	125	9			98			350
	80% SW	830	252	14			227			
Reptilia										
Alligator	FW	276	140	3.6	5.1	3.0	111			
Aves									1.6	
Anas (duck)	FW	284	138	3.1	2.4		103			
Mammalia										
Homo sapiens	Ter.		142	4.0	5.0	2.0	104	1	2	
Lab rat	Ter.		145	6.2	3.1	1.6	116			

*SW = seawater; FW = fresh water; Ter. = terrestrial.

†The osmolarity and composition of seawater vary, and the values given here are not intended to be absolute. The composition of body fluids of osmoconformers will also vary, depending on the composition of the seawater they are tested in.

Sources: Schmidt-Nielsen and Mackay, 1972; Prosser, 1973.

theme of an excellent book by the late Homer Smith (1953) entitled *From Fish to Philosopher*.

Although there may be hourly and daily variations in osmotic balance, an animal is generally in an osmotic steady state over the long term. That is, on the average, the input–output balance sheet over an extended period sums up to zero (Figure 12-2). Water enters with food and drink, and in a freshwater environment it enters primarily through the respiratory epithelium—the gill surfaces of fish and invertebrates, and the integument of amphibians and many invertebrates. Water leaves the body in the urine, in the feces, and by evaporation through the integument and lungs.

The problem of osmotic regulation does not end with the intake and output of water. If that were so, osmoregulation would be a relatively simple matter: A frog sitting in fresh water far more dilute than its body fluids would merely have to eliminate the same amount of water as leaked in through its skin, and a camel would just stop urine production between oases. Osmoregulation also includes the requirement of maintaining favorable solute concentrations in the extracellular compartment. Thus, the frog immersed in hypotonic pond water is faced not only with the need to eliminate excess water, but also with the problem of retaining salts, which tend to leak out through the skin.

Exhibit C

EXERCISE AND ITS PHYSIOLOGY

BY

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AND

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·e structures is obviously, in descending
and lastly nerve fiber. *Local fatigue is*
the motor end organ.
in mammals by immobilizing the animal
the motor nerve continuously while the

the motor end organ is fatigued earlier than
muscle preparation of a frog. A, fatigue of
otor nerve; B, fatigue record of the same
e muscle directly, obtained immediately and

artificial respiration. After some hours
the kidneys and the muscles supplied by
anus. The infatigability of nerve may
nt. It may be shown that this remains
many hours of stimulation. One needs
at the action current follows contempo-
d is an external means of demonstrating

iven before is the conventional explana-
this line of reasoning may seem to be, a
atigue has arisen following the work of
his theory of *chronaxie* (page 62). It
he waste products of muscular activity,
the chronaxie of the muscle two or three
(strength of stimulus required) (1 and
unaltered. As soon as the chronaxie of
the nerve fibers which innervate it, the
rve impulse is lost. It is obvious that
no longer *isochronal*, but are different,
heterochronism. The nerve impulse with

its unaltered chronaxie will not stimulate the muscle with its altered and quite different chronaxie. After a sufficient interval has elapsed for the muscle to recover from fatigue, its chronaxie will again be found to have regained its original value. When this condition is attained the muscle may again be stimulated through its motor nerve. On the other hand, if the chronaxie of the muscle is decreased by some other means than by allowing the proper interval of rest for recovery, the muscle will similarly respond since there is established a more or less complete state of isochronism. The chronaxie of muscle may be reduced by the application of adrenalin (3). It is generally known that adrenalin facilitates the recovery from fatigue whether in an isolated muscle or in the living body. The facts just cited not only offer a possible explanation of fatigue, but explain the beneficial action of adrenalin in offsetting this condition (Chapter XXV).

If this recent view stands the test of time, the conventional conception of fatigue of the motor end organs must take on a new light. We are probably justified in tentatively accepting such an explanation of peripheral or muscular fatigue.

The cause of muscular fatigue.—Recalling at this time what has already been said (Chapters III and IV) relative to the changes which occur in muscle as it responds to a stimulus, we may state that muscle contraction is a mechanical end response of the entire process and serves as an index to other internal changes which precede it. The chemical changes involve a cleavage of the precursor glycogen (anærobically) into an equivalent amount of lactic acid which is rapidly neutralized by the local muscle buffers. This reaction releases a definite and prescribed quantity of energy which may appear in part as work and in part as heat or, when no work is done, appears *in toto* as heat. In recovery the acids are removed; in part being oxidized (ærobically), in part being resynthesized into glycogen.

It is generally conceded that two factors may be involved in the production of muscular fatigue. Fatigue may be due to a depletion of the immediately available glycogen precursor or to the accumulation of the waste products of the non-oxidative reaction. It has been repeatedly shown that the muscle glycogen is diminished in amount in proportion to the duration and severity of the activity, but it has been demonstrated equally well that fatigue may occur at a time when the glycogen stores are far from being exhausted. This is particularly true in extreme forms of activity where fatigue sets in rapidly. Moderate activity extending over relatively long periods is more likely to be associated with a greater glycogen depletion. *The chief and immediate cause of fatigue is usually the accumulation of the waste products, especially lactic acid.* During very short but strenuous forms of activity one may become fatigued and completely recover many times in the course of a day without exhausting the muscle-glycogen stores.

It has been known since 1865 (Ranke) that the injection of dilute solutions of lactic acid, carbonic acid or mono-potassium phosphate into isolated muscles produces immediately and mimics exactly all of the outward signs

chronaxie by Lapicque. Slowly responding muscles are innervated by slowly conducting nerves and *vice versa*, and both have correspondingly long or short chronaxics. They have the same chronaxie, that is, there exists a state of *isochronism*.

The waste products of activity increase the chronaxie of muscle but not that of nerve fibers. This state of *heterochronism* renders excitability of the former through the latter impossible. Rest restores the state of *isochronism; adrenalin* will do so more quickly.

The immediate cause of muscular fatigue in strenuous forms of activity is the accumulation of waste products within the active muscles, namely, lactic and other acids; in moderate and light forms of activity, fatigue may result from the exhaustion of the muscle glycogen. The acids produced anærobically are quickly neutralized by the *muscle buffers*. When these are exhausted, the reaction of the muscle becomes more acid and further activity is temporarily suspended—the muscles are fatigued. Proper nutritive and circulatory conditions and also training may alter the buffering capacity of the muscles.

Muscle contraction is dependent upon the liberation of lactic acid; relaxation upon its removal. For prompt response, the latter is then dependent upon the immediate neutralization of the acids by the buffers. In fatigue this phase of muscle contraction is affected most.

If a sufficient interval is allowed between responses, recovery occurs simultaneously and the muscles are able to respond for an indefinite period without fatigue. Once completely fatigued a period of approximately two hours is necessary for complete recovery. If during this period further effort is attempted, the period of recovery is greatly prolonged. Any condition which interferes with or improves the nutritive condition of the muscles will diminish or augment the efficiency and amount of work obtainable. When time is considered, there is an optimum load for each muscle. Fatigue of one group of muscles diminishes the amount of work obtainable from another. Mental work or effort produces a similar effect.

QUESTIONS

1. What prevents the self-inhibition of cell activity?
2. Describe an experiment to show the relative infatigability of the nerve fiber.
3. Where is the seat of local muscular fatigue?
4. Define chronaxie, isochronism, and heterochronism.
5. What is the effect of lactic acid on the chronaxie of muscle and of nerve?
6. What is the action of adrenalin on a neuromuscular preparation?
7. What two factors are involved in muscular fatigue?
8. What is the chief cause of fatigue?
9. Write the chemical equations indicating glycolysis.
10. Discuss the muscle buffering of lactic acid.
11. How much lactic acid may the intact muscles form per second and how much may be formed as a maximum?
12. What is the *p*H of a normal muscle; of a completely fatigued isolated muscle?

13. What determines the m
contain at any given time?
14. Explain how carbon diox
15. Upon what chemical cha
16. Explain how a slight ri
in muscles.
17. What is the effect of exh
18. What are the principal fi

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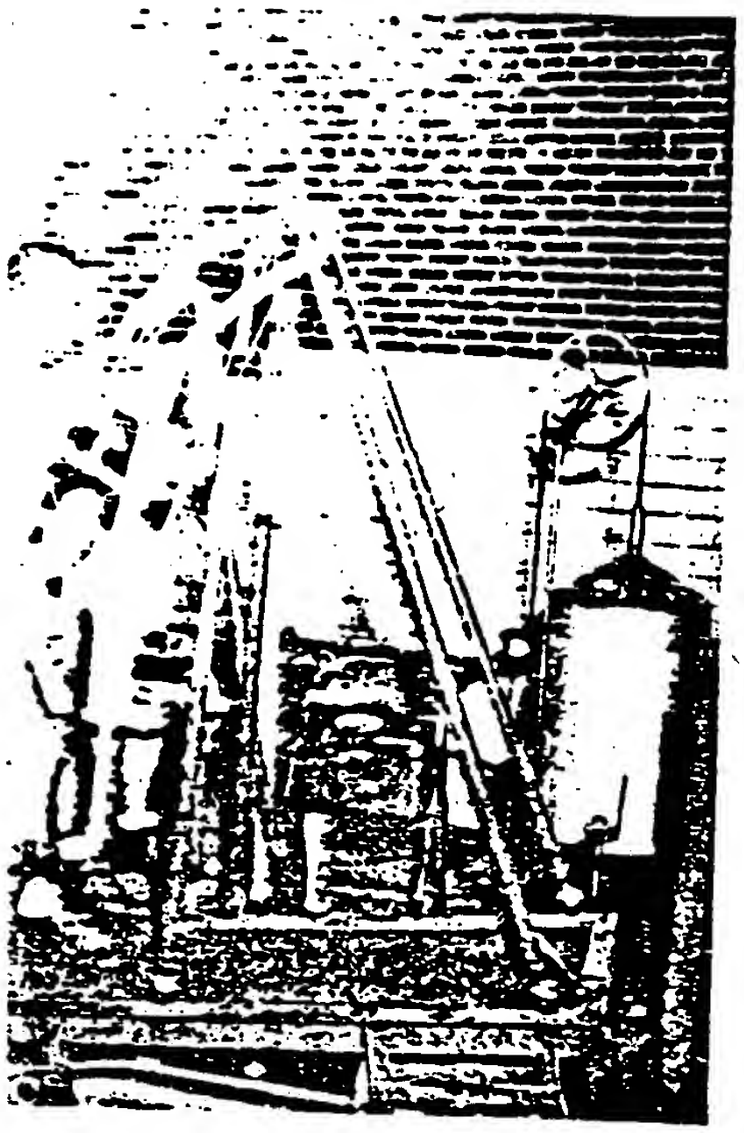

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PHYSIOLOGY OF EXERCISE

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hat the ratio of $NaHCO_3$ to H_2CO_3 o normal. A numerical example may conditions may be represented by a f 7.40. Assume that a large quantity

in exercise and that 10 per cent of posed in buffering the lactic acid. A nic acid is formed and the ratio ation of the Henderson-Hasselbalch

pH of 6.88. There is now an actual is diminished and the pH is lowered. ted, breathing is increased and a larger nated until finally the ratio $\frac{NaHCO_3}{H_2CO_3}$ y the same as the ratio $\frac{20}{1}$ so that

wever, the alkali reserve is still below factor, the kidney. undertakes the reting a more acid urine. The base ine is retained in the blood and the ed to normal. Several days may be process.

is still another physiological factor, dation and resynthesis of lactic acid esses result in release of the alkali he lactic acid immediately following

ulation in Exercise

s formed by the contracting muscles id. So long as the oxygen supply is accumulation of lactic acid in the the first several minutes of moderate adjustments have become adequate a produced, but when a steady state is mulation of acid. The only acid-base e is the elimination of carbon dioxide

and due to the great diffusibility of this gas it is improbable that this process is ever inadequate.

When the oxygen requirement of exercise exceeds the supply, lactic acid accumulates in the contracting muscles and diffuses into the blood. According to Owles[1] there is for each individual a critical level of activity above which lactic acid accumulates. The critical level varies among individuals and in the same individual for different types of exercise and different degrees of training. The determining factor seems to be the efficiency with which oxygen can be supplied to the muscles.

The fate of the lactic acid which diffuses into the blood is not entirely clear. If it enters the blood very rapidly, as in short bursts of violent activity, some of it is excreted in the urine. This is a mixed blessing, since it involves the loss from the body of that much glycogen precursor. Some of the blood lactic acid is removed from the blood flowing through inactive muscles, but it is not certain that it is here reconverted to glycogen. It may simply be stored temporarily to be returned slowly to the blood during the recovery process. It is highly probable that the bulk of the lactic acid which is poured into the blood is removed by the liver where the major portion of the resynthesis to glycogen takes place.

The extent to which accumulation of lactic acid in the contracting muscles serves to limit their activity is controversial. Even in the so-called resting state muscles are probably never entirely free of lactic acid. The resting level is approximately 0.015 per cent and is in the form of sodium or potassium lactate having been neutralized by the tissue buffers. This "resting" level of lactic acid concentration is due to the facts that muscles are never completely at rest and that the oxidation of lactic acid in low concentrations is exceedingly slow.

In isolated muscles contraction fails completely when the lactic acid reaches a concentration of about 0.30 per cent, the "fatigue maximum." The tissue buffers are inadequate for the neutralization of this much acid so that the acidity of the muscle increases to a point at which activity is impossible. It is probable that a similar concentration of lactic acid would put an end to muscle contractions in the body, but it is also probable that in most cases other factors, such as the blood supply to the heart, would result in cessation of

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...exercise experiment on a motor-driven treadmill. ...gen from the small gasometer at the right, ...collected in the large gasometer at the left. ...diotachometer which records the heart rate. ...ro periodic measurement of blood pressure. ...blood are followed by analyzing finger-prick ...mical methods.

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PHYSIOLOGY OF EXERCISE

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tests (omitting emotional factors). A well-trained athlete may be able to absorb 4 liters of oxygen per minute and to acquire an oxygen debt of 15 liters. It has been firmly established that, when the maximum oxygen debt has been incurred, the body becomes incapable of further effort. These facts permit one to estimate the duration of exertion which is possible when the oxygen requirement is greater than the maximal oxygen intake.[7] Assume that an athlete is able to absorb 4 liters of oxygen per minute and to incur an oxygen debt of 15 liters. If he runs at a speed requiring 5 liters of oxygen per minute, he must go into debt for oxygen at the rate of 1 liter per minute, and this intensity of exertion could be sustained for 15 minutes. If the speed of running is increased until the oxygen requirement is doubled, the excess of oxygen requirement over oxygen intake is 10 – 4 — 6 liters per minute, and exhaustion would occur at the end of 15 6 — 2.5 minutes.

In running, the oxygen requirement increases as the square or cube of the speed. Therefore doubling the rate of running, from an initial level requiring 4 liters of oxygen per minute, increases the oxygen requirement per minute from 4 to 8 times. A man does not have time to incur his maximal oxygen debt in short sprints. It has been estimated that 50 to 55 seconds of running at top speed would be required before the maximal oxygen debt would be reached.

Since the maximum amount of exertion which is possible before exhaustion occurs is determined by the upper limits of the oxygen intake and the oxygen debt, the question naturally arises as to the factors which set these limits. The factors limiting oxygen intake will be discussed in later chapters. The factors which set the upper limit of the oxygen debt have not been definitely established. In an isolated muscle of a frog, stimulated electrically, contraction ceases when the concentration of lactic acid has risen to about 300 mg. per 100 grams of muscle. It is possible that the accumulation of lactic acid also determines the limit of muscular activity in a human being—at least an increase in the blood lactic acid concentration to about 200 mg. per 100 ml. of blood is usually associated with exhaustion. It is uncertain whether, and to what extent, depletion of ATP may contribute to the limitation of exertion.

Influence of Training on Oxygen Rec and Oxygen Debt.—The results of tra briefly as follows:

1. The oxygen requirement for a giv result of more efficient use of muscles i ous movements and of greater mechan cles themselves.

2. The maximal oxygen intake is inc capacity of the heart to pump blood an respiratory adjustments.

3. It has been claimed that training oxygen debt which can be reached. due to an increase in the amount of buf ing lactic acid, to an increase in the ar cles, or perhaps to a greater ability to the discomfort of impending exhaustio

A more complete discussion of the found in Chapter 22.

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Physiology of Muscular Activity

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Causes of Fatigue

The primary cause of fatigue, both mental and physical, must be activity involving the expenditure of energy by the body, as there is no fatigue when all expenditure is excluded. Such a state is rest. Fatigue of either type is chemical in character. It may be the result of (1) a depletion or nonavailability of stores of energy in the body; or (2) the accumulation of end products of metabolism which become a hindrance to vital exchanges of the body; or (3) an alteration of the physiochemical state, a breakdown of homeostasis.

1. The fact that fatigue can be delayed by the administration of sugar to men during hard physical labor is sufficient evidence that a reduction in the store of energy-producing substances is a causative factor.

2. The end product or waste product theory of fatigue was suggested by the nineteenth-century German physiologist, Ranke, when he found that certain substances formed during contraction depress or inhibit the power of muscle contraction. Among these products are lactic acid, carbon dioxide and acid phosphates. It should be noted that the extent of the occurrence of some of these substances depends in part on the inadequacy of the oxygen supply to the muscles during their activity. Oxygen is required for the chemical processes within an organ. There is no simpler way of hastening fatigue than to subject the individual to a diminished oxygen supply.

Products causing fatigue may arise in ways not ordinarily thought of as connected with the output of energy. They sometimes enter the blood stream as a result of disturbances of digestion or because of poor ventilation, which may lead to inhalation of noxious gases.

3. When the average man finishes his day's work, his fatigue cannot be ascribed to a specific fatigue substance, to hypoglycemia or to anoxemia. We must fall back on some other sort of explanation.

4. Changes in the internal environment, the physiochemical state of the blood and lymph, may also cause fatigue. A large number of delicately interrelated substances cooperate in maintaining the balanced condition of these fluids. A marked increase or decrease in any one of the substances may modify the fluids sufficiently to affect adversely the living cells of the

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Textbook of Work Physiology

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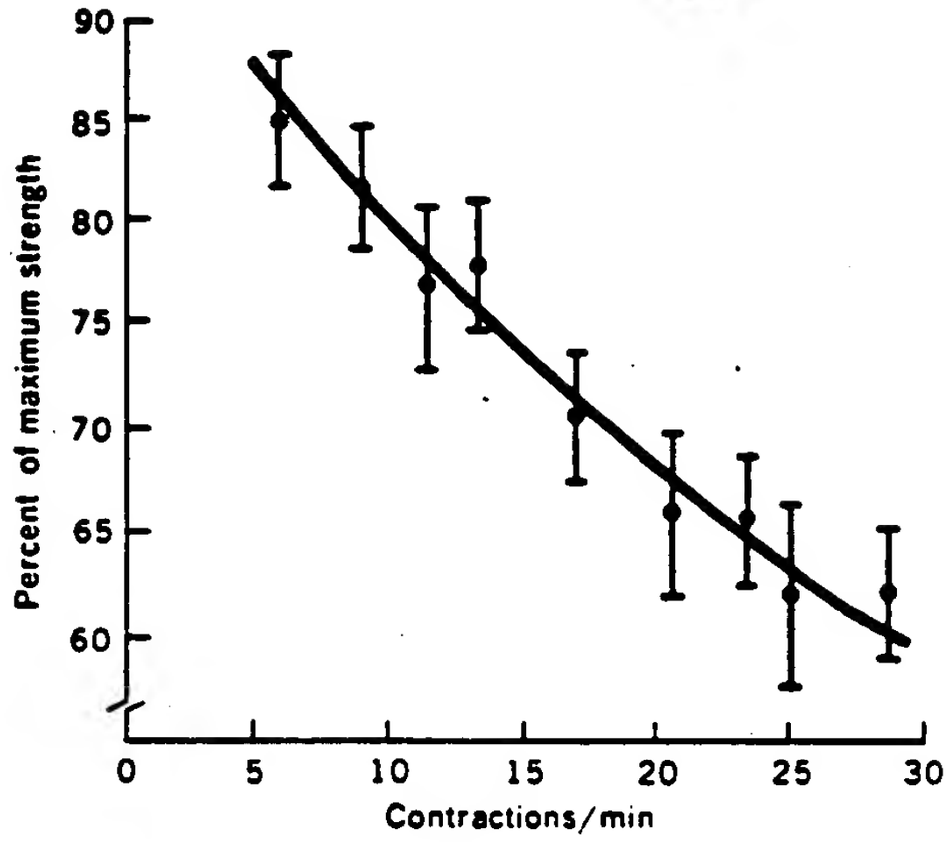

Fig. 4-29 Percent of maximum isometric strength that can be maintained in a steady state during rhythmic contractions. Points are averages for finger muscles, hand muscles, arm muscles, and leg muscles, combined. Vertical lines denote ± standard error. (Molbech, 1963.)

lishes the blood flow (Merton, 1954; Royce, 1958). Metabolites and carbon dioxide can be washed away from the muscle, and the oxidative restoration of the energy-producing mechanism is reestablished. Dynamic contractions also periodically hinder the passage of blood, partly or totally. The work load, in relation to the duration of the contraction periods, and the intervals between the periods of contraction determine the length of time the work can be endured. In exercises including frequent dynamic concentric contractions, the energy output for a given tension is relatively high. According to Asmussen, this type of exercise can probably be performed for long periods of time only if the developed strength does not exceed 10 to 20 percent of the maximal isometric strength.

Figure 4-29 shows results from experiments in which the subjects performed rhythmic maximal isometric contractions on a dynamometer in pace with a metronome (Molbech, 1963). Gradually the tensions decreased because of fatigue, but they finally leveled off at a value that could be maintained for a long time. With 10 contractions/min, about 80 percent of the maximal isometric strength could be applied without impairment. With 30 contractions/min the maximal load was reduced to 60 percent. The values seemed to be independent of the size of the activated muscle group.

Apparently the ability of the muscle fibers to maintain a high tension and the individual's subjective feeling of fatigue are highly dependent on the blood

flow through the muscle. In very short spells of work, ATP and creatine phosphate can yield energy and the oxygen present in the muscle (bound to the myoglobin) also makes an energy delivery from aerobic processes possible. A prolonged activity period with reduced blood flow may cause the oxygen need to exceed the oxygen supply, and the anaerobic processes must contribute markedly to the energy yield. The impaired blood flow not only limits the oxygen supply but also the removal of metabolites and heat. Exactly which factor limits the performance is not known. It could be an accumulation of lactic acid, of H^+, and/or heat. With appropriately spaced pauses, the blood flow can secure the supply of oxygen and energy-rich compounds and wash out the produced substances, and the work can proceed aerobically for long periods of time.

Effect of prolonged exercise In heavy exercise prolonged for hours the work output during maximal efforts becomes gradually decreased (Saltin, 1964). After 1 hr rest, a work load that normally could be tolerated for 6 min had to be terminated after about 4 min due to exhaustion. The peak lactate level in the blood was correspondingly decreased. It is believed that the limiting factor must be sought at the cellular level in the exercising skeletal muscles, and could be anything from a change in the properties of the membrane of muscle fibers, a disturbed ATP-ADP "machine," etc., to a depletion of the glycogen stores or a reduced capacity to neutralize the metabolites produced.

Nöcker (1964) points out that prolonged exercise to exhaustion decreases the potassium concentration within the active muscle cells, e.g., from 635 to 460 mg 100 ml in rats. An increase in the hydrogen ion concentration increases the permeability of the cell membrane. The coupled $Na^+ - K^-$ pump may be less efficient in prolonged activity of the muscles. Since the potassium-sodium balance is of the utmost importance for the excitability and the recovery of the muscle fibers, it is reasonable to assume that the muscle's decreased ability to contract can be linked to a *disturbed ion balance*, eventually, with a hyperpolarization of the cell membrane. There is also a possibility of modifying the afferent impulses from a muscle subjected to prolonged severe exercise with an increased inhibition of the motoneurons as a consequence. In emergency situations this inhibition can, however, eventually be inhibited. A direct stimulus of the fatigued muscle (prolonged work) has increased the force of contraction in some experiments.

There are *characteristic changes of the EMG* in muscle fatigue, indicating a change in both the impulse traffic in the motor nerve and the muscle reaction to the discharge. The amplitude increases and the rhythm slows down. A grouping and synchronization of the discharges appears which, at least partly, can be attributed to a decrease of the proprioceptive afferent impulses from muscle spindles, as shown by Kogi and Hakamada (1962). These authors found that the quotient of the electrically integrated amplitude of slower components divided by that of the faster components increased gradually and steadily in fatigue experiments of isometric-isotonic contractions of various strength. The appearance of a high "slow wave" ratio was significantly related to the onset of a local fatigue sensation, to the feeling of pain, and to the subject's incapability of maintaining the intended tension.

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PHYSIOLOGY OF EXERCISE AND SPORT

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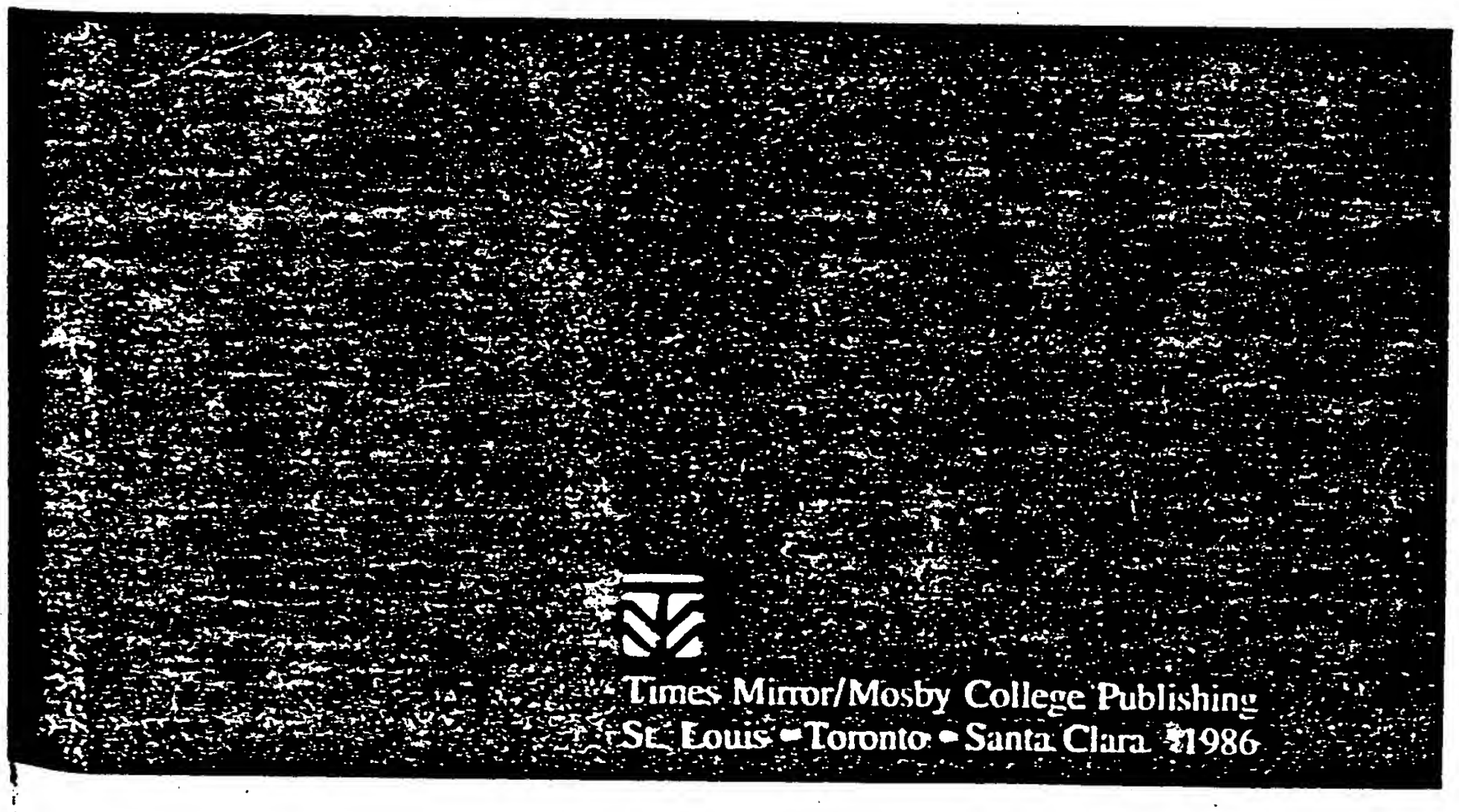
With 165 illustrations



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We know that the production of ATP by glycolysis results in the production of lactic acid. Very high levels of lactate within muscle following maximal exercise have been reported.[34] These cause a rapid decline in both muscle pH and blood pH.[19] Phosphofructokinase (PFK) is the rate-limiting enzyme in the glycolytic pathway and is known to be inhibited by low pH.[23] Low pH may also inhibit further production of ATP anaerobically, thus causing muscle fatigue. It has been suggested that increased H ion concentration caused by high lactate production may decrease the effect of Ca^{++} on troponin, thus reducing tension generation.[23] Although it is tempting to accept this very plausible explanation, the problem of muscle fatigue is not completely solved. Considerably more experimental evidence is required to provide indisputable validation.

Peak anaerobic power output and genetic influence

Muscular strength and power have been included in genetic studies of monozygous and dizygous twins.[40] Muscular strength, measured as maximal isometric knee extension, did not show a significant between-twin variation between the two twin types. Therefore, there is no high heritability estimate for this variable. Power was estimated by the Margaria stair-running test[44] and recorded in kg-meters/sec. Here, significant variability between the twins was observed between male twin groups. The heritability estimate was 97.8, indicating a very high genetic component. It appears that whereas muscular strength is highly susceptible to training, muscular power (ATP-PC) is less susceptible because of the genetic influence.

Anaerobic power summary

Anaerobic power can be defined as the maximal ability of the anaerobic systems (ATP-PC + lactic acid) to produce energy. The ATP-PC system can be measured directly, but it requires invasive techniques (muscle biopsy). Indirectly, this system can be estimated by recording peak power output (kg-meters · sec^{-1}) over a short period of time, less than 10 seconds. The ability of the lactate system can be indirectly estimated by pedaling at a maximal rate for 30 seconds on a bicycle ergometer (Wingate test) or by performing continuous maximal contractions for 60 seconds on an isokinetic device. Such a test characterizes what can be called anaerobic decay or the decline of peak power output over time. EPOC, previously explained by the *oxygen debt* hypothesis developed by A.V. Hill and later modified, has been found to be inadequate. EPOC is not related to lactate conversion as predicted by the hypothesis. It has been suggested that fatigue during anaerobic exercise may be related to the accumulation of lactic acid, which decreases pH, in turn inhibiting glycolysis and decreasing the effect of Ca^{++} on troponin, which reduces tension generation. Peak anaerobic power output (ATP-PC) has been found to have a very high genetic component (97.8).

KEY TERMS

aerobic power the maximal amount of oxygen that can be consumed per minute during maximal exercise.

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The Physiological Basis of Physical Education and Athletics

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mechanism itself. Some of them are as follows:

(a) *Accumulation of Lactic Acid.* Fatigue due to lactic acid accumulation has been suspected for many years.[18, 25, 31, 32, 33] However, only recently has a relationship between intramuscular lactic acid accumulation and decline in peak tension (a measure of fatigue) been established.[17, 49] This relationship is shown in Figure 5–22*A* for isolated frog sartorius muscle[17] and in Figure 5–22*B* for intact human vastus lateralis muscle.[49] Whereas establishment of these relationships does not in itself prove conclusively that lactic acid causes fatigue, it does lend considerable support, which has been lacking in the past, to the idea. For example, in the classic experiments conducted by A. V. Hill and colleagues over 50 years ago[25] from which the hypothesis that lactic acid causes muscular fatigue originated, lactic acid accumulation in the muscle was never even measured!

The lactic acid accumulation in the human vastus lateralis is represented as the ratio of lactic acid concentrations in FT and ST fibers (horizontal axis of Figure 5–22*B*). This means that as the ratio increases, more lactic acid is being produced in FT fibers in comparison with ST fibers. This greater ability to form lactic acid might be one contributing factor to the higher anaerobic performance capacity of the FT fibers.[49] Notice also that as the lactic acid FT:ST ratio increases, the peak tension of the muscle decreases. This may be interpreted to mean that the greater fatigability of FT fibers is related to their greater ability to form lactic acid.

The idea that lactic acid accumulation is involved in the fatigue process is further strengthened by the fact that there are at least two physiological mechanisms whereby lactic acid could hinder muscle function. Both mechanisms depend on the effects lactic acid has on intracellular pH or hydrogen ion (H^+) concentration. With increases in lactic acid, H^+ concentration increases and pH decreases. (More on pH and acid-base balance is presented in Chapter 21, p. 551.) On one hand, an increase in H^+ concentration hinders the excitation-coupling

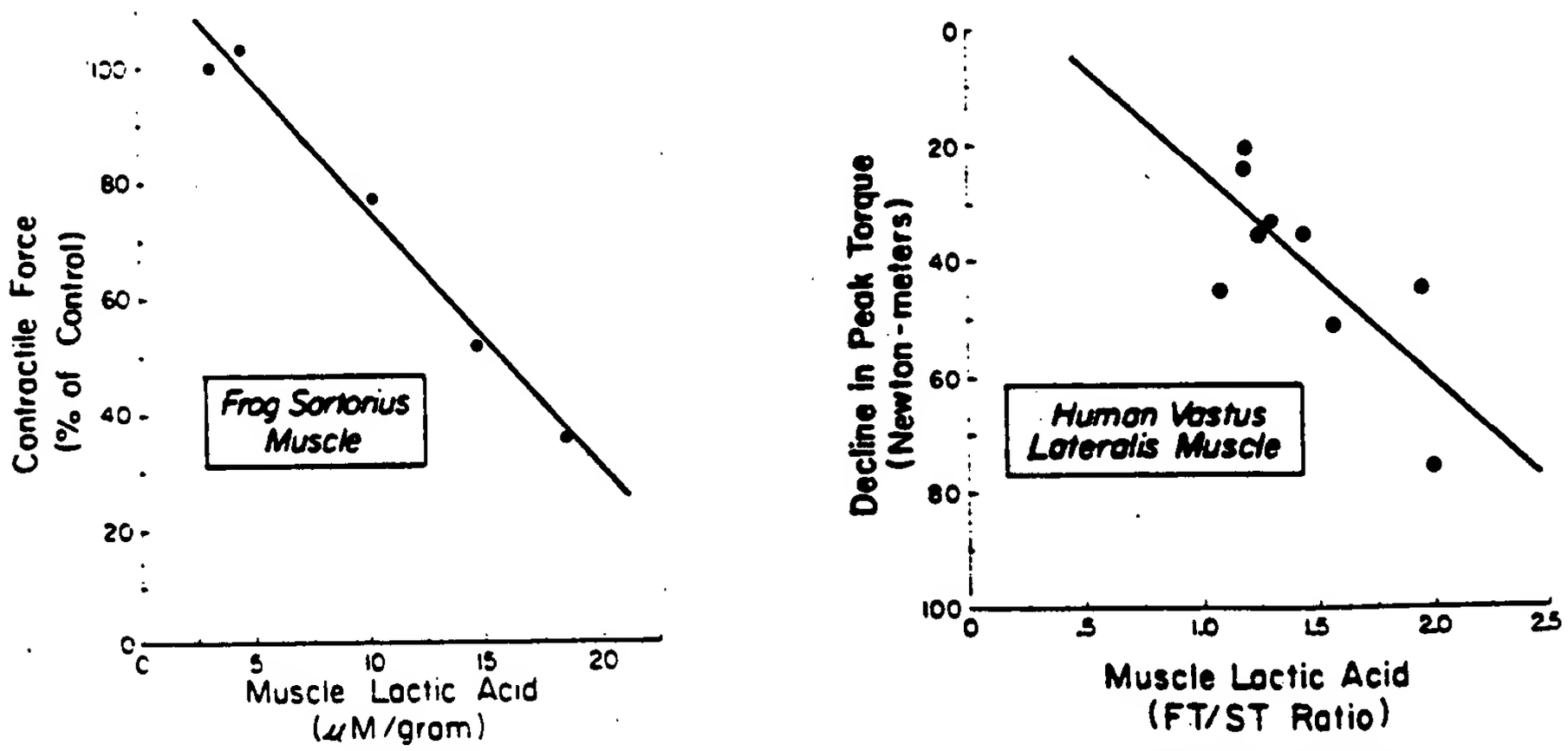

Figure 5–22. *A.* Relationship between intramuscular accumulation of lactic acid and decline in peak tension (a measure of muscular fatigue) for isolated frog sartorius muscle and, *B.* for intact human vastus lateralis muscle. (Data in *A* from Fitts and Holloszy;[17] data in *B* from Tesch et al.[49])

SECOND EDITION

PHYSIOLOGY OF EXERCISE

RESPONSES & ADAPTATIONS

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Fatigue in Activities That Can Be Sustained Between 10 Seconds and 2–3 Minutes. For exercise that can be sustained for longer than 10 seconds but less than about 2–3 minutes, a substantial drop in creatine phosphate stores (perhaps greater than 90 per cent) can be measured along with a 30–40 per cent decrease in ATP [6, 23, 35]. Because much of the ATP seems to be stored in the mitochondria, the sarcoplasmic reticulum, and in other compartments, a rather small fraction of the ATP is available for muscle contraction. Therefore, it appears that creatine phosphate depletion may limit the ability of the muscles to sustain contractions at these high loads. Another factor to consider is that lactic acid accumulates rapidly during intensive exercise of short duration and may contribute to fatigue. As lactic acid is produced in anaerobic glycolysis, it causes a reduction in the intracellular pH of the muscle to values as low as 6.4, compared to an intracellular pH at rest of about 7.0 [46]. At such a low pH, the activity of phosphofructokinase, an important enzyme in glycolysis, is markedly reduced. Therefore, the replenishment of ATP by glycolysis may also be reduced when lactic acid builds up with strenuous exercise. Thus, for exhaustive exercise sustained between 10 seconds and 2–3 minutes, the likely causes of fatigue are creatine phosphate depletion and lactic acid accumulation.

Fatigue in Activities That Can Be Sustained Between 3 and 15 Minutes–The Case for Lactic Acid as a Fatigue Factor. Physical exercise that can be sustained for 3–15 minutes does not seem to be limited by depletion of either ATP, creatine phosphate, or glycogen. Although there is a large fall in creatine phosphate levels in the muscles, this reduction is similar for exercise that can be sustained for 6–7 minutes and for exercise lasting 20–25 minutes [35]. (See Fig. 15.4.) Accordingly, if creatine phosphate depletion were the limiting factor for this type of exercise, it should be impossible to continue working beyond 6–7 minutes. Muscle glycogen falls by only 10–30 per cent in work of less than 15 minutes' duration [49]. Therefore, since it is widely agreed that neither fat nor blood glucose makes a significant contribution to activity that leads to exhaustion in less than 15 minutes, it seems that some factor other than depletion of energy reserves limits exercise of 3–15 minutes' duration. Perhaps lactic acid accumulation is that factor.

Lactic Acid Accumulation in Muscles. The theory that lactic acid accumulation in the muscles limits muscular performance has been widely held since at least 1935 [50]. There are several reasons why this idea has achieved such popularity. With

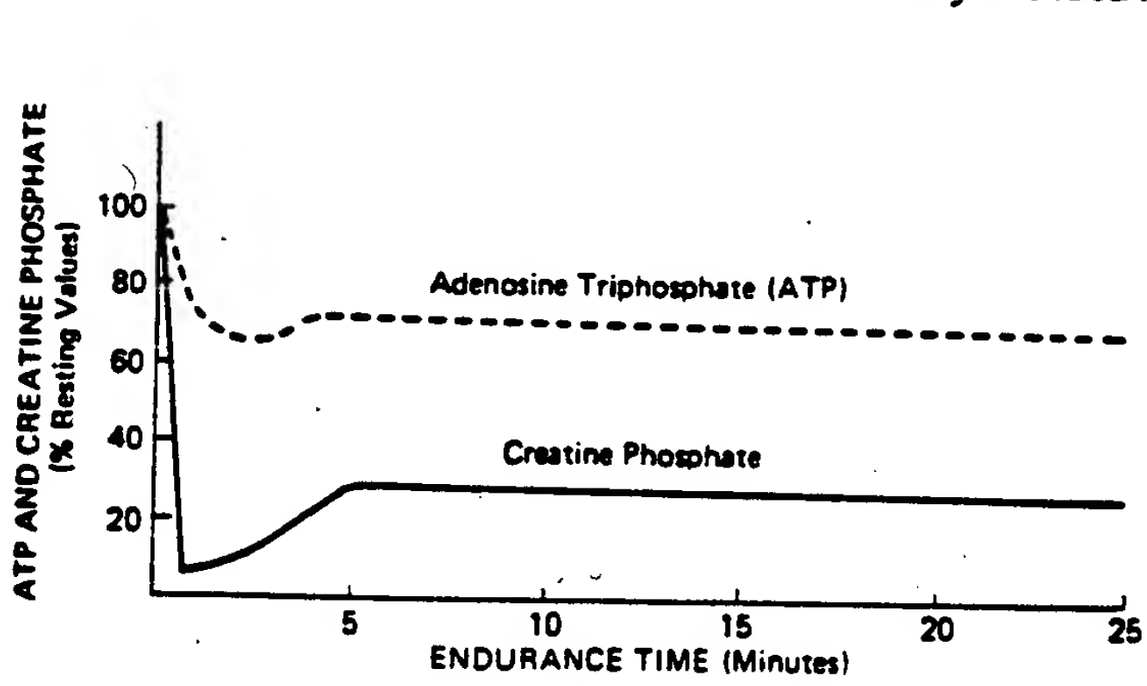

FIGURE 15.4. ATP and creatine phosphate depletion with exercise sustained for 1–25 minutes. Data primarily from reference 35.

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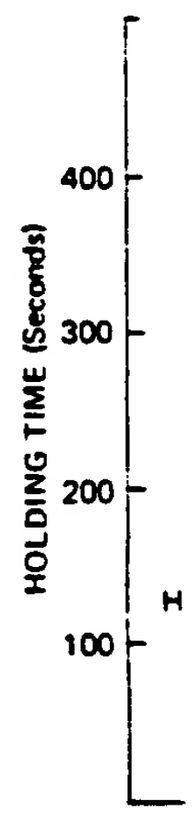

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most types of heavy exercise, fatigue is associated with high levels of lactic acid, and the *rate* of lactic and pyruvic acid accumulation in the working muscles is very closely related to the intensity of contractions [2]. This relationship is shown in Fig. 15.5; it demonstrates that the time one can hold an isometric contraction decreases with increasing load and increasing *rate* of acid accumulation in the muscle. Other evidence which supports the idea that the accumulation of lactic acid leads to fatigue is the strong relationship between the concentration of lactic acid in muscle and the time course of fatigue development and recovery [19, 20, 36]. As illustrated in Fig. 15.6, the force produced by a muscle progressively decreases as lactic acid concentration increases; also, the force generated progressively recovers as lactic acid concentration is reduced. It has also been shown that fatigue with the legs occurs earlier if previous exercise with the arms has raised the circulating lactic acid level in the blood [52].

The effect of lactic acid on promoting early fatigue is probably the result of the accumulation of hydrogen ions (H+), which lowers the pH of the muscle [19, 46, 47, 48]. One of the effects of such a reduction in pH is a decrease in the binding of calcium to troponin, thereby reducing the activation of actin-myosin cross bridges in muscle contraction [7, 11, 19, 23]. Also, several key enzymes of glycolysis, including glycogen phosphorylase and phosphofructokinase, are inhibited by excess acidity [6, 23, 46]. This means that less ATP can be replenished by glycogen breakdown when lactic acid levels are high. Finally, it has been shown that if body fluid pH is made more acidic by the consumption of ammonium chloride capsules before exercise, exercise endurance is markedly diminished; however, upon administration of sodium bicarbonate (an alkaline substance), endurance is increased [33]. Thus, there is a large body of evidence that lactic acid accumulation is causally related to fatigue in exercise of 3–15 minutes' duration.

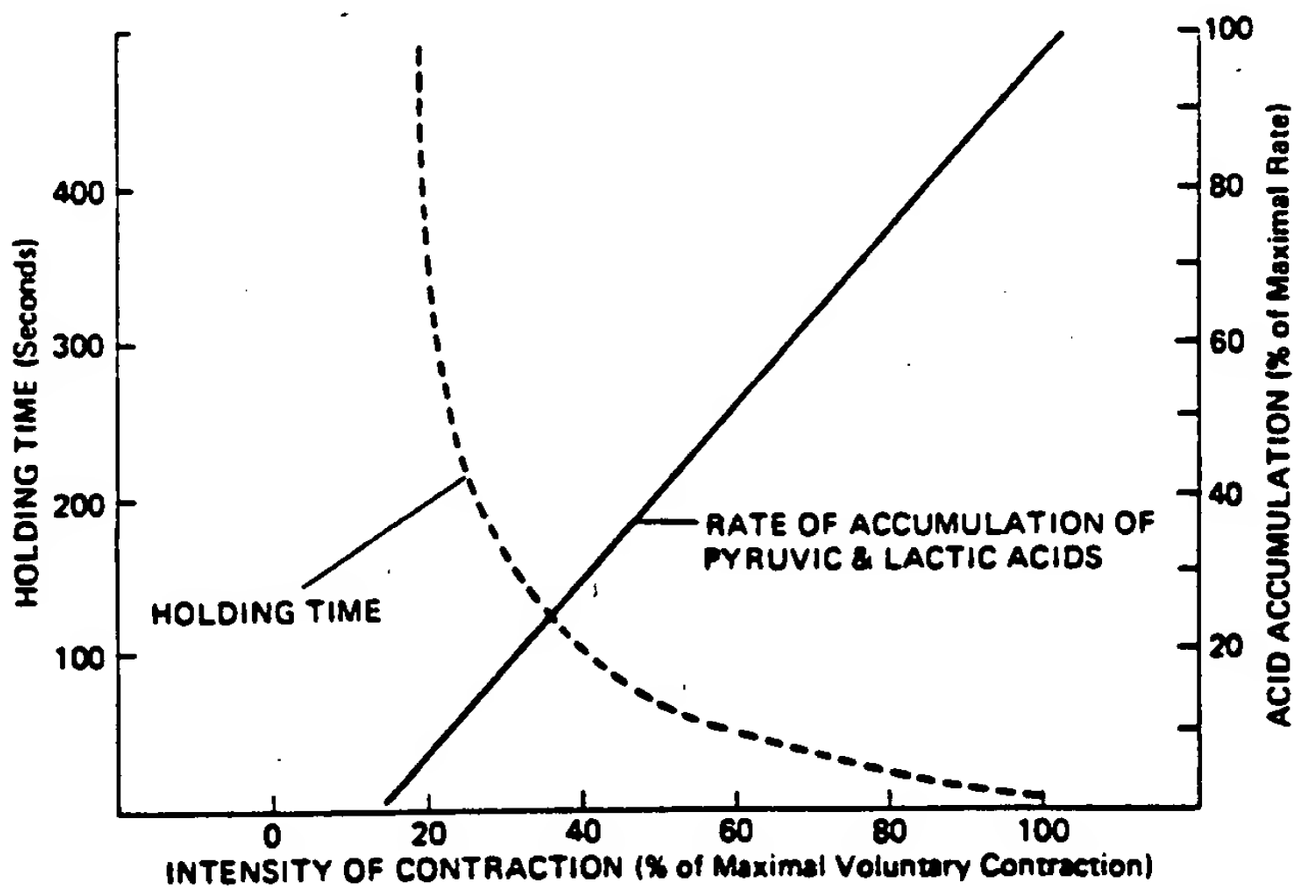

FIGURE 15.5. Isometric contraction holding times and rates of accumulation of lactic and pyruvic acids at various intensities of muscular contraction. Data from reference 2.

EXERCISE AND ITS PHYSIOLOGY

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selves and to the sodium salts of the muscle proteins. We may express these reactions by the following equations:

(1) $CH_3.CHOH.COOH + Na_2CO_3 \rightarrow NaOOC.CHOH.CH_3 + NaHCO_3$
Lactic acid — Sodium carbonate — Sodium lactate (NaL) — Sodium bicarbonate

For simplicity we may designate the lactate ion by L, thus in the following pages NaL will be employed to designate sodium lactate. Theoretically the reaction shown above would be possible, but probably sodium carbonate never actually exists in the tissues in the presence of acids but only in the form of the bicarbonate, thus, using the simplified formula:

(2) $C_3H_6O_3 + NaHCO_3 \rightarrow NaL + H_2CO_3$
Lactic acid — Sodium bicarbonate — Sodium lactate — Carbonic acid

For the buffer reactions of the muscle phosphates we have:

(3) $C_3H_6O_3 + Na_2HPO_4 \rightarrow NaL + NaH_2PO_4$
Lactic acid — Disodium phosphate — Sodium lactate — Mono-sodium phosphate

Similarly for the salts of muscle proteins we have:

(4) $C_3H_6O_3 + \text{Na proteinate} \rightarrow NaL + \text{H proteinate}$
Lactic acid — Sodium proteinate — Sodium lactate — Acid proteinate

Meyerhof (9) has shown that probably ninety per cent or more of the acid is neutralised by the muscle proteins. Lactic acid or its lactate equivalent is probably never completely absent in living muscle. This is what might be expected from the nature of chemical reactions and the *mass law*. From the data available on this point (Fletcher and Hopkins and others), we are safe in concluding that the probable minimum of lactic acid in resting muscle is about 0.015 per cent. This value may be increased to twenty times this figure (0.3%) following strenuous activity. Hill (8) has shown that the muscles of the entire body may produce as much as from three to four grams of lactic acid per second in the most strenuous forms of exercise and that the total quantity of this acid present in the muscles at any one given time may amount to 130 grams. More will be said about this in the chapter on recovery.

We may learn more about the buffering capacity of muscles from a study of isolated muscles such as the gastrocnemius of the frog. When an isolated muscle is suspended in a weakly alkaline saline or Ringer's solution, the lactic-acid maximum which may be reached is considerably higher. Furthermore, it has been shown that the highest lactic-acid values may be reached when the solution is not only alkaline but contains phosphates (Meyerhof). Under these conditions, even in the absence of oxygen, glycolysis may run to completion, that is, continue until the store of glycogen is completely exhausted. Lactic-acid values as high as 0.827 per cent have been found by

Meyerhof (9). If instead of the alkaline phosphate the acid phosphate (NaH_2PO_4) had been employed in the solution, this value would drop to 0.097 per cent.

The conclusion to be drawn from these results is that in the first case, alkaline phosphate has diffused into the muscle and there increased the buffering capacity to a level above that normal for it; in the second case, some of the alkaline buffers usually present in the muscle diffuses out into the solution while the acid phosphate diffuses inward. It seems equally obvious that the maximum of lactic acid which a muscle can contain at any given time is determined by its content of the buffers described previously. It would further seem to follow from this fact that the presence of lactic acid tends to prevent its further formation, that is, when the acid reaches a certain concentration, glycolysis is completely inhibited. It will be shown in Chapter IX that the presence of this acid also tends to accelerate the rate of its removal. This again is in accordance with what might be expected if the change is governed by the laws of chemical reactions and the *mass law*. The katabolic cleavage of glycogen into lactic acid would then, if left to itself, soon run to self-inhibition. On the other hand, in the absence of glycolytic cleavage practically complete removal of lactic acid would take place.

The reaction of muscle and the principle of buffers.—Lactic acid is a relatively strong acid, being ten per cent ionised at the maximum concentration at which it occurs in the body. Since the strength of any acid is a function of its dissociated hydrogen ion and not the quantity of the acid, lactic acid is relatively stronger than carbonic acid which is less completely ionised at the concentrations at which it is found in the body. On the other hand, the alkaline carbonates and phosphates available for its neutralization are poorly dissociated and, hence, weakly alkaline. Since the capacity of an alkali to neutralize an acid is not dependent upon its immediate state of ionization, that is, its true state of alkalinity, but upon the total amount of alkali present, there exists in muscle a high potential capacity for neutralization at a maintenance of a low hydroxyl ion (OH) concentration. The symbol *p*H is used to denote hydrogen ion concentration (Chapter XIII). The relatively strong lactic acid readily reacts with the available alkali with the final result that from the highly ionised acids only slightly ionised acids and acid salts (carbonic acid and mono-potassium phosphate) are formed. Because of the fact that the burden of the hydrogen ion is now carried by weakly dissociated acids or acid salts, the reaction of the muscles remains almost unchanged. The reaction of a normal muscle is about *p*H 7.2; complete fatigue produced by stimulation of an isolated muscle cannot lower it much below *p*H 6.7 (Hill).

This is fundamentally the principle of chemical buffers. It is because of the presence of such a mechanism in our muscles that we are able to perform activities of more than a few moments' duration. This fact will be treated in greater detail in another place. It may be said that our power of endurance

is no greater than the capacity of our muscle buffers, but it will be shown later that this is not the only factor which limits the amount of work our muscles can endure.

Just as the lactic-acid maximum is not always the same in isolated muscles, but depends upon the conditions of the experiment such as the nature and composition of the solution in which the muscle is bathed or the nature, amount, and composition of the blood supplying the muscle in the intact individual, so also the lactic-acid maximum may vary from time to time in the intact body. It is not at all improbable that the buffering power of the muscles may vary from individual to individual, or within the same individual under various states of nutrition and training.

If this assumption is true, which seems highly probable, it will account, in part at least, for the variations among men in their capacity to do work, a fact which is so well-known that we need not discuss it further at this time. We may further find in it a partial explanation of the value of training in preparation for competition for the performance of a certain piece of work or of the value of proper exercises to keep one fit and in good physical condition. We are all familiar with the fact that under such conditions we have better breath ("wind"), we are under less strain for the completion of a given task and we do not fatigue so quickly or when fatigued we recuperate more readily. This improved buffering capacity is only one of the many factors in the process of training.

Non-oxidative production of carbon dioxide.—It is of further interest that when alkaline carbonates serve as the buffers there is always a certain formation of carbonic acid, see reaction 2 above. This reaction is non-oxidative and takes place anærobically. Carbonic acid, however, being a weak acid is, because of this fact alone, of somewhat less significance in producing an acid reaction of the muscle than is lactic acid itself. Again carbonic acid is more readily diffusible and it tends, because of differences of concentrations of tensions, to pass from the tissues into the blood. The manner in which it is carried by the blood and its influence on respiration and respiratory exchange will be discussed in Chapters XIV and XVI. From the blood it is readily lost in the lungs and is passed out in the exhaled air as carbon dioxide. The method of transfer between the blood and air in the alveoli of the lungs is again one of diffusion due to concentration gradients.

The importance of muscle buffers in the mechanics of muscular contraction.—The rapid and rather complete neutralisation of the lactic acid is a very important phenomenon. In the first place, if our assumption as stated in Chapter VI is well-founded and correct that the changes in tension developed during muscle contraction are brought about by virtue of the action of the hydrogen ion of the lactic acid on the local muscle structures, then before relaxation can occur these ions must be neutralized. This must also be consummated quickly with relatively no "hold-over" or the relaxation phase will become delayed and longer in duration.

We are now in a position to view the development of fatigue from a slightly different point of view. Any condition which will delay either the formation of lactic acid from its precursor glycogen or its neutralisation will consequently diminish the rate of the mechanical response and at the same time prolong all phases of a single muscle twitch. We are now also in a better position to understand more clearly why an increase or decrease in temperature will accelerate or diminish, respectively, the rate of response in muscles. Contraction is dependent upon the liberation of hydrogen ions on the surfaces of the muscle structures (cleavage of glycogen into lactic acid) while relaxation is dependent upon its neutralization by the muscle buffers. Since the temperature coefficient of the former is 2.5 for each rise of ten degrees C. and for the latter 3.6, it is obvious that temperature changes will affect the relaxation phase to a greater extent than that of the contraction. It is because of this fact that cold slows the relaxation phase considerably more than the other phases of the response. On the other hand, *"warming up"* shortens it so that it more nearly corresponds in time duration with that of the contraction phase.

It is well at this time to recall the phases of a muscle twitch and their relative durations (page 34). This decreased relaxation time due to a slight rise of temperature becomes of further importance as fatigue develops since fatigue products act in such a way as to prolong this phase of the muscle response. Any rise of temperature during the process of the development of fatigue will accelerate to a somewhat greater extent those chemical reactions involved in the neutralisation and ultimate removal of the lactic acid. In this light, a slight rise of temperature may exert an appreciably beneficial effect in delaying the onset of fatigue.

The chemical basis of fatigue.—An adequate explanation of fatigue must be sufficiently inclusive to give a satisfactory answer to the many known and accepted phenomena which are related to this condition. It must explain why a muscle fatigues more quickly in the absence of oxygen than in its presence, also more quickly in an atmosphere of nitrogen; why an isolated muscle fatigues sooner than one left in the intact animal; why irrigation of an isolated muscle with saline or weakly alkaline solution facilitates recovery; why injections of lactic or carbonic acids bring on fatigue almost immediately; and why the exhaustion of the glycogen store will produce fatigue as readily as the presence of waste products. In the light of what has been said in the preceding pages, we are in a position to state at least some of the fundamental factors involved in the production of fatigue.

It may be recalled that the first requirement of muscle in its response is the liberation of a quantity of free energy which is the driving force, so to speak, for the mechanical response to follow. This comes from the anærobic breakdown of glycogen into lactic acid and the interaction of the latter on the surfaces of the contractile structures of the muscles. It scarcely needs to be repeated that unless there is a source of available glycogen in the muscles

there can be no formation of lactic acid and hence no free energy released. Under these conditions a state of fatigue may exist in which there is a low concentration of lactic acid in the muscle and even while the muscle reaction remains quite unchanged. It has been shown earlier, however, that fatigue may set in before the glycogen store is exhausted. Although the absence of glycogen in the muscles may bring about a condition of fatigue, this is not the usual and immediate cause. It is only in activity of long duration that the muscles are liable to be exhausted of their glycogen. The usual cause of fatigue is the accumulation of the waste products. This is invariably the case in all forms of strenuous exercise of short duration.

In moderate activity we are able to continue without rest for relatively long periods of time without complete fatigue. This is due to the fact that the waste products are being removed almost as rapidly as they are formed. With more strenuous forms of activity, on the other hand, we may become fatigued within a few minutes or even seconds, depending upon the rate of activity. The difference between the underlying changes which are occurring within the muscles is a quantitative one only in which the lactic-acid-formation phase greatly exceeds that of its removal. It is now clear that this will soon exhaust the buffering capacity of these tissues. They will become more acid in reaction due to the unneutralised acid which being in solution is free to ionize. *It may be said that just as soon as the muscle-buffering capacity becomes exhausted and the reaction of the muscle reaches a certain acidity* (pH), *due to lactic and other acids, further response becomes impossible.*

There are, of course, various stages in the development of fatigue varying in intensity from a mild form in which the acting muscles are sluggish and response is difficult to more complete fatigue in which there is inability to respond. The retention of the acid metabolites in excess of that capable of ready and immediate neutralization by the tissue buffers will greatly delay the onset and course of the relaxation phase, hence, the muscles act slowly and are more sluggish. It has also been shown that these products alter the *chronaxie* of muscle, but not that of nerve and in so doing bring about a state of *heterochronism* between the two so that stimulation of the muscle through its nerve becomes possible. Furthermore, it has been shown that the presence of the acid cleavage products of glycogen inhibit that cleavage, hence, depress or abolish the mechanism through which the energy for contraction is liberated. In a true sense then we may say that activity in and of itself tends toward self-inhibition.

Mosso's ergograph.—By means of a specially devised apparatus—the ergograph (Fig. 32)—or work recorder, Mosso (6) was able to study the development of fatigue in the human subject and to determine the influence of various external and internal conditions upon the quantity of work, efficiency of the human machine, and the temporary and probable lasting effects upon the individual. These are not only of theoretical but of practical importance and apply to most types of work and activity alike, whether in an athletic event or in the various forms of labor common to all forms of industry. A brief statement of his principal findings is worthy of consideration at this point. The muscle generally employed for these studies is the flexor muscle of the second finger (M. flexor sublimis digitorum, Fig. 33).

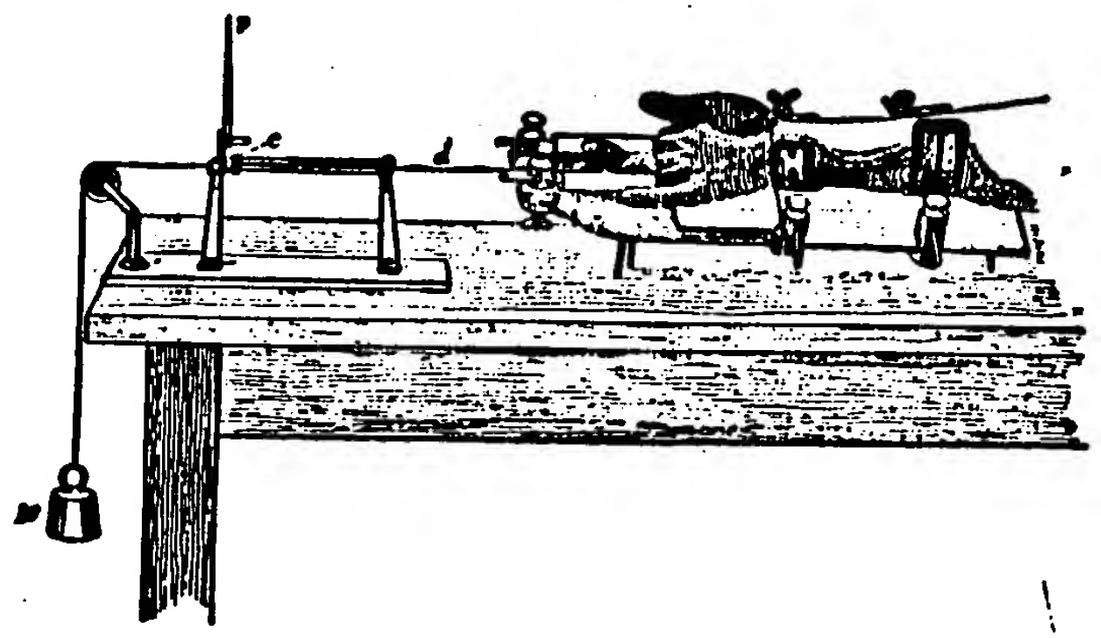

FIG. 32—Mosso's ergograph: *c* is the carriage moving to and fro on runners by means of the cord *d*, which passes from the carriage to a holder attached to the last two phalanges of the middle finger (the adjoining fingers are held in place by clamps; *p*, the writing point of the carriage, *o*, which makes the record of its movements on the kymographion; *w*, the weight to be lifted. (From Howell, *Textbook of Physiology*, by courtesy of W. B. Saunders Company.)

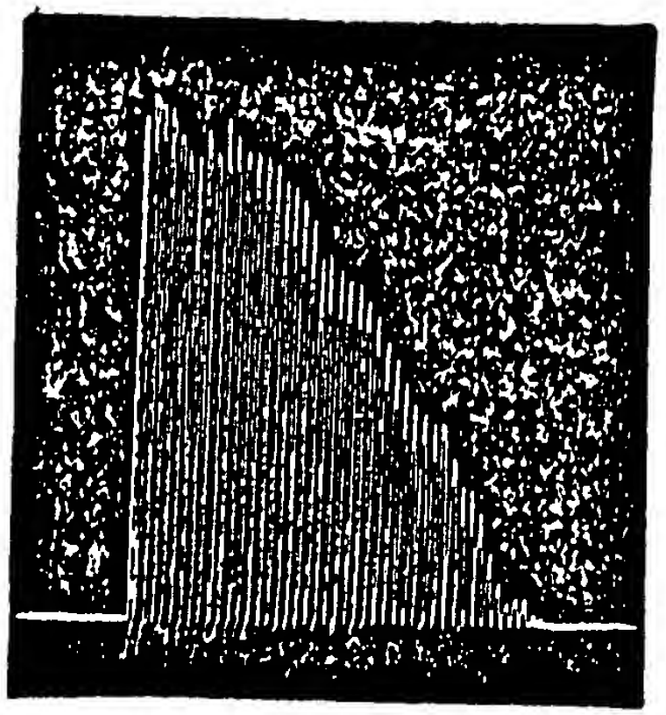

FIG. 33—Fatigue curve of flexor of middle finger of right hand lifting a weight of three kilograms. Contractions at intervals of two seconds.

1. With a given load the rapidity with which fatigue develops and the amount of work which can be done by a muscle depends largely on the number of contractions elicited in a given time. This is shown by the data presented in the following table:

TABLE I

(Modified from Zoethout, *Textbook of Physiology*, The C. V. Mosby Co.)

Interval between contractions, in seconds	Number of contractions necessary to produce fatigue	Work accomplished in kgms.
1	14	0.012
2	18	1.080
4	31	1.842
10	no fatigue	almost indefinite

For every load there is a certain rate at which the most work can be accomplished in a given time. If the rate of contraction is too rapid it will diminish the total number of responses possible and, hence, diminish the work done; while if too slow, although fatigue does not occur, the output of work is also reduced. Crowding a large amount of work into short periods is, therefore, uneconomical even though long rest intervals intervene (Table II). This may be considered a "lazy man's" recompense.

TABLE II

(From Zoethout, *Textbook of Physiology*, The C. V. Mosby Co.)

Rate	Number of contractions	Duration of test period	Work done in kgms.
15 every 30 mins.	420	14 hrs.	26.9
60 every 120 mins.	420	14 hrs.	14.7

2. If successive responses are made at sufficiently long intervals, no fatigue signs are apparent. This interval is about ten seconds for the muscle indicated above. This period is fairly constant for any given muscle, but may vary from muscle to muscle, and may be affected in any single case by various nutritive and other bodily conditions.

3. Once a given muscle is fatigued a certain rest interval is necessary for its complete recovery, that is, until it is fully capable of producing a response similar to that from which it is recovering. For the flexor muscles of the fingers this is about two hours. For other muscles the interval may be different, but in any case is rather constant under normal conditions.

4. If further effort is made to continue work before a fatigued muscle is completely recovered, a relatively greater rest period will be required to restore it to normal. Moreover, even if the muscle is strained without producing any external movement or work, this may also be true.

5. Any condition which interferes with or improves the nutritive condition of the muscle or body as a whole will diminish or increase the efficiency and amount of work obtained from the muscles. Loss of sleep, hunger, mental distress, mental activity, anxiety, anemia, and other diseases diminish the power of the muscles to perform work. On the other hand, proper sleep and rest, proper food, adequate circulatory conditions, massage, and moderate exercise all tend toward a better performance of the muscles.

6. More work can be accomplished with small loads than with large ones. When a muscle is completely fatigued by a heavy load, it is yet capable of continuing its response if given a lighter one.

7. Fatigue of one group of muscles, as those of the legs in running, will diminish the amount of work which can be done with another group, as those of the arm.

8. After mental activity a sensation of fatigue is felt in the body generally. Mental fatigue diminishes the amount of work which can be obtained from the muscles. In one instance, the subject was able to lift a three-kilogram weight forty-eight times before becoming fatigued and in thus doing performed 7.16 kilogrammeters of work; on another occasion, after delivering a lecture, this same individual was only able to lift this same weight thirty-eight times with a performance of 5.06 kilogrammeters of work. Whatever the cause of mental fatigue may be, it is obvious that mental fatigue is not relieved by physical exercise. In Mosso's own words, "It is, therefore, a physiologic error to interrupt lessons to make children do gymnastics in the hope that this may diminish brain fatigue. The best way to rest is to sit still and think of nothing and let children play about and amuse themselves in the open air." Similarly one cannot hope to obtain maximal performance of an athlete or of anyone who is preparing to perform physical work if he is mentally fagged. The nervous effort to drive the activity gradually increases—the curve of nervous effort is the reverse of the curve of muscle performance.

Summary

It is a striking principle in biology that activity of living cells tends to produce an inhibition of that activity. This imposes upon the organism a period of rest adequate for its recovery. Naturally our interest in fatigue of the human body centers upon the muscles and the nervous system. For purposes of description, we may distinguish between *muscular* and *nervous fatigue;* the former to designate that of the peripheral muscle with its motor nerve, the latter that of the central nervous system.

Of the peripheral structure, *nerve fibers* are relatively infatigable. The *junctional tissue* between muscle and nerve is fatigued sooner than the *muscle fiber*. Muscular fatigue then resides in the so-called *motor end plate*.

Stimulation of a tissue is not only dependent upon the strength but also the duration of the stimulus. This duration factor has been designated

chronaxie by Lapicque. Slowly responding muscles are innervated by slowly conducting nerves and *vice versa*, and both have correspondingly long or short chronaxies. They have the same chronaxie, that is; there exists a state of *isochronism*.

The waste products of activity increase the chronaxie of muscle but not that of nerve fibers. This state of *heterochronism* renders excitability of the former through the latter impossible. Rest restores the state of *isochronism; adrenalin* will do so more quickly.

The immediate cause of muscular fatigue in strenuous forms of activity is the accumulation of waste products within the active muscles, namely, lactic and other acids. In moderate and light forms of activity, fatigue may result from the exhaustion of the muscle glycogen. The acids produced anærobically are quickly neutralized by the *muscle buffers*. When these are exhausted, the reaction of the muscle becomes more acid and further activity is temporarily suspended—the muscles are fatigued. Proper nutritive and circulatory conditions and also training may alter the buffering capacity of the muscles.

Muscle contraction is dependent upon the liberation of lactic acid; relaxation upon its removal. For prompt response, the latter is then dependent upon the immediate neutralisation of the acids by the buffers. In fatigue this phase of muscle contraction is affected most.

If a sufficient interval is allowed between responses, recovery occurs simultaneously and the muscles are able to respond for an indefinite period without fatigue. Once completely fatigued a period of approximately two hours is necessary for complete recovery. If during this period further effort is attempted, the period of recovery is greatly prolonged. Any condition which interferes with or improves the nutritive condition of the muscles will diminish or augment the efficiency and amount of work obtainable. When time is considered, there is an optimum load for each muscle. Fatigue of one group of muscles diminishes the amount of work obtainable from another. Mental work or effort produces a similar effect.

QUESTIONS

1. What prevents the self-inhibition of cell activity?
2. Describe an experiment to show the relative infatigability of the nerve fiber.
3. Where is the seat of local muscular fatigue?
4. Define chronaxie, isochronism, and heterochronism.
5. What is the effect of lactic acid on the chronaxie of muscle and of nerve?
6. What is the action of adrenalin on a neuromuscular preparation?
7. What two factors are involved in muscular fatigue?
8. What is the chief cause of fatigue?
9. Write the chemical equations indicating glycolysis.
10. Discuss the muscle buffering of lactic acid.
11. How much lactic acid may the intact muscles form per second and how much may be formed as a maximum?
12. What is the pH of a normal muscle; of a completely fatigued isolated muscle?

13. What determines the maximum amount of lactic acid which a muscle can contain at any given time?
14. Explain how carbon dioxide may be non-oxidatively produced in muscles.
15. Upon what chemical change is relaxation dependent?
16. Explain how a slight rise in temperature may delay the onset of fatigue in muscles.
17. What is the effect of exhaustion of the muscle-buffering capacity?
18. What are the principal findings of the ergograph concerning fatigue?

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11. What is probably the effect of the suprarenal hormone on muscles and their activity?

12. Discuss the relation of fatigue to inhibition.

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CHAPTER IX

THE RECOVERY PROCESS IN ISOLATED MUSCLE

Strictly speaking there is no time during the life of man or any other animal at which we may say all forms of activity are suspended completely. Even during so-called rest the metabolic processes of the body cells are in progress although at a minimum level, in fact in these processes we have one of the criteria by which we are able to distinguish living from non-living things. The activities of the muscles, glands, and other structures are dependent upon the basically fundamental metabolic processes of their constituent cells. During the so-called periods of activity of any organ the metabolism which is characteristic of it is increased in proportion to the degree of the activity. The metabolic processes during the activity are essentially similar to those during periods of rest, but quantitatively may vary considerably. Furthermore, one phase of the metabolic process may be affected to a much greater extent than others.

In the same sense that there is no state of absolute inactivity, there is also no time when the process of recovery is not in progress. From the point of view of the physiology of activity and recovery, this fundamental concept is of first importance. Similarly, the recovery process during the so-called inactive periods is fundamentally of the same nature as that during periods of activity, differing mainly in degree. Both activity and recovery are relative.

It may be concluded that a period of activity in any living cell, organ or individual, no matter how brief, is followed by a period of recovery from that activity which is in excess of the resting level. This recovery is essentially a process of reconstruction in which the waste products of the excess metabolism are removed and the conditions within the cells are brought to their normal so-called resting state. When the activity is very brief, as in a single response or reflex, recovery occurs subsequent to the active state, lasting, however, for only a brief interval; when it is more prolonged, recovery proceeds as the action continues. No matter how long or how short the activity, however, there is always a phase of recovery which is delayed. This is implied in the fact that activity must always precede recovery else there would be no recovery. In brief, it may be said that recovery always lags behind.

Conventional usage has restricted the term *recovery* more or less definitely to the reconstructive or anabolic processes which follow recognized forms of bodily activity and particularly physical activity. This viewpoint of the recovery process will be stressed more particularly in this chapter because of its fundamental and practical importance. There are, however, mechanisms

provided in our active tissues for a more temporary type of recovery and by virtue of which continuous activity for relatively long periods is made possible. These are intimately interrelated with the more commonly known forms of response generally included under the caption of activities and deserve brief mention here.

The recovery of irritability.—All living things, muscle, nerve, and other body tissues not excepted, are irritable, that is, they are capable of being excited to perform their own specific type of activity when stimulated. It has been shown in Chapter V that during stimulation certain characteristic changes occur within the muscles and nerves which are fundamental to the development of activity,—also that for a brief interval following the application of the stimulus the tissue is completely inexcitable to a second stimulus, *absolute refractory period*, after which it gradually regains its normal excitability, *relative refractory period*, and may even pass through a period during which its excitability may be from twenty to thirty per cent supernormal. In the strictest sense this is truly a process of recovery having its beginning at the onset of the relative refractory phase. Just why there should be a period of supernormal irritability cannot be satisfactorily explained as yet. Its importance lies in the fact that if the stimuli are so timed as to fall in this period, the maximal response becomes greater and more efficient. It is probable that an explanation of the true treppe or staircase phenomenon lies in this supernormal phase.

The total refractory period is in the neighborhood of 0.0006 second for nerve and 0.005 second for muscle. Since Adrian (1) has found that the rate of return of excitability is increased approximately three times for nerve and four times for skeletal muscle by a rise of temperature of ten degrees C., the underlying processes of excitation and recovery must be chemical in nature. This period of recovery from the refractory state in both nerve and muscle is so brief as to never become a limiting factor in determining the rate of response in man. It is complete in these tissues before the onset of the mechanical response of the skeletal muscles involved. It is because of this fact that summated and tetanic contractions are possible in this form of muscle. The relative refractory state of heart muscle, however, is coterminus with the relaxation phase and thus in the living individual there can be no summated or tetanic response of this organ. Even in compound or tetanic contraction of skeletal muscles, under which category the greater part of our muscle responses fall, the interval between the separate nerve impulses discharged from the central nervous system is relatively long (approximately 0.02 second) and, hence, succeeding impulses would fall upon tissue having fully recovered from any previous refractory state.

Recovery in the absence of oxygen.—A more obvious type of immediate or temporary recovery from activity is to be found in the buffering of the lactic and other acids which are formed during the anærobic phase of muscle response. It is through this mechanism that the acids may be temporarily neutralised as a guarantee of the rapid removal from the field of action, otherwise they would tend to inhibit further immediate response. Moreover, because of this mechanism activity may proceed in the absence of or in excess of the immediate supply of oxygen (Chapter X).

Changes Which Occur in Muscles During Recovery

In order to understand to best advantage the significance of the changes which occur in muscles during recovery, it may be well to recall the changes which have occurred within them during the development of fatigue. They may be listed briefly as follows: (1) muscle glycogen is diminished in amount; (2) lactic acid has accumulated in the muscles principally in the form of sodium lactate; (3) the muscle carbonates are diminished in amount; (4) heat has been liberated in proportion to the lactic acid formed; (5) certain organic phosphoric-acid-containing compounds have been hydrolyzed yielding phosphoric acid (page 45); and (6) the free H ions (true acidity) have risen to a point at which activity is no longer possible—fatigue has developed.

So long as an isolated muscle is kept under anærobic conditions lactic acid continues to accumulate until the process runs to self-inhibition. Immediately, however, it is placed in an atmosphere containing oxygen, certain definite changes occur within it: (1) the lactic acid diminishes relatively rapidly; (2) muscle glycogen is increased in amount; (3) oxygen is consumed in amounts proportional to the lactic acid removed; (4) a further liberation of heat results which is approximately equal to that liberated during the anærobic period; (5) the organic phosphoric-acid-containing compounds are reformed; and (6) the free acidity falls and normal irritability and contractility return. The process is essentially a reversal of the anærobic phase outlined in the preceding paragraph. Because of the relatively small magnitude of these changes in a single response and because of the complicating factors associated with repeated responses, they are difficult to study and analyse. With our present-day methods, however, studies of the thermal changes have been very fruitful in revealing the intimate nature of muscular contraction and the subsequent recovery process.

Recovery and heat production.—In their study of the thermodynamics of contracting muscle, Hartree and Hill (2) and Hill (3a) have shown that in the absence of oxygen heat production rises quickly during the latent period and contractile phase; that there is a further liberation of heat during the relaxation phase, and a slow evolution of heat for two to three minutes following the completion of relaxation (Chapter IV). This delayed heat production amounted to approximately twenty-five per cent of that evolved during the total response (initial heat). If now the evolution of heat is measured in the presence of oxygen (ærobic), the total heat is approximately twice that developed in its absence (anærobic). The heat evolved after the completion of the response is now approximately one and one-half times that produced during the response making the true recovery heat about one and one-fourth

times this value. In this we have a measure of the magnitude of the recovery process.

The evolution of the recovery heat rose rapidly at first, two to three minutes, then fell off more slowly and finally ran to a termination after about ten minutes. Granting that the evolution of this recovery heat is coterminous with the process of recovery, the latter then is not complete for some minutes after the termination of the response.

The importance of oxygen to the recovery process.—The nature of the local recovery process can be studied to best advantage in isolated muscles. It will be recalled from what has been said in the preceding paragraphs that muscles are able to respond for a limited time even when completely deprived of oxygen. Under these conditions there can be no permanent recovery and once fatigued they remain in this condition until *rigor* sets in. When the acid concentration reaches a certain level, from 0.2 to 0.3 per cent, they no longer respond to stimuli—they are fatigued. As the acid concentration rises the muscles slowly shorten and pass into the so-called state of *rigor* (*rigor mortis* or *death stiffening*). Any condition which will accelerate the rise of lactic acid in the muscles (chloroform, caffein, previous activity) greatly accelerates the onset of rigor.

The limited period of anærobic response is made possible solely by virtue of the muscle buffers; once these are exhausted further anærobic activity is impossible although lactic acid may continue to be formed. Were it not for the presence of this buffering mechanism the duration of muscular activity in the absence of oxygen would be extremely brief. When, however, a muscle is placed in an atmosphere containing oxygen it soon regains its irritability and contractility—it has recovered. Furthermore, the period of activity is greatly prolonged under ærobic conditions since the recovery process is going on simultaneously with the activity. If the activity is mild or moderate in character it may continue for a long time, being limited only by the oxygen and glycogen supplies.

In isolated muscles the supply of oxygen depends upon the thickness of the muscle, in thick ones the diffusion of this gas into the innermost fibers requires too long an interval and since the superficial fibers are, so to speak, rabid for oxygen those farther removed may suffer. In the living body, conditions are quite different since the muscles receive their oxygen from the blood of the muscle capillaries. These are so numerous as to make the distance of diffusion exceedingly small and, hence, serve admirably in bringing the much needed oxygen to the muscles (page 351).

In an isolated muscle there is sufficient oxygen dissolved in its fluids for complete recovery from a single twitch or even a short tetanus. When, however, the supply of available oxygen drops below the level of the demand, the recovery process is retarded; in other words, the rapidity of the recovery is proportional to the oxygen supply. In the human body where the oxygen is supplied by the blood, the oxygen supply may be said to be adequate for mild and even moderate forms of activity, but inadequate for more strenuous

exertions. It is not to be inferred, however, that the oxygen consumption is proportional to its supply; it is only when the substances to be oxidised are in excess that the recovery rate can be determined by the oxygen supply. The speed of recovery in oxygen has a high temperature coefficient and therefore is dependent upon chemical reactions. *Recovery depends primarily upon the process of oxidation.*

The oxidative reaction may be represented by the following equation:

$$\underset{\text{Lactic acid}}{C_3H_6O_3} + \underset{\text{Oxygen}}{3O_2} \rightarrow \underset{\text{Carbon dioxide}}{3CO_2} + \underset{\text{Water}}{3H_2O}$$

For each molecule of oxygen used one molecule of carbon dioxide is formed. The respiratory quotient (R. Q.) or ratio $\frac{CO_2}{O_2}$ of such an implied recovery process is unity. This is in agreement with the assumption that carbohydrate is the immediate and only food utilized by isolated muscles. The possibility of other food substances being employed as sources of muscle energy will be discussed in a subsequent chapter. If any other food substance were oxidized, the respiratory quotient would be less than unity (page 156).

The ratio of oxygen consumption to the lactic acid removed.—If the oxygen which is required to completely oxidize one gram of lactic acid *in vitro* is compared with that necessary to cause the removal of one gram of the same acid within the muscles there arises a most striking discrepancy. In the living muscle, one gram of this acid requires approximately 150 cubic centimeters of oxygen for its removal, in other words, one liter of oxygen would serve to remove from six to seven grams of lactic acid *in vivo*. From the equation just given, it is clear that since the molecular weight of lactic acid is 90, and three molecules of oxygen are required to oxidise one molecule of the acid, one gram-molecule of lactic acid (90 grams) will require three times 22.4 liters or 67.2 liters of oxygen for its complete oxidation. One gram-molecule of a gas under standard conditions occupies 22.4 liters. From these values it may be calculated that 746.7 cubic centimeters of oxygen will be required to oxidise each gram of lactic acid. Obviously the entire gram of lactic acid could not have been oxidised in the tissues. The ratio of lactic acid oxidised to lactic acid removed is only $\frac{150}{746.7}$ or approximately $\frac{1}{5}$. For every gram of lactic acid oxidized, approximately four grams are disposed of in some non-oxidative manner.

This was at one time a puzzling fact, but since first established it has been shown that during recovery the glycogen content of similar surviving muscles is greater under ærobic than under anærobic conditions. In one of his typical experiments, and during a survival of forty-five hours, Meyerhof (4) found a carbohydrate loss equivalent to 1.17 milligrams of glycogen or 1.3 milligrams of glucose or lactic acid per gram of muscle in an oxygen atmosphere as compared to 3.375 milligrams and 3.75 milligrams respectively per

gram for a similar muscle in nitrogen. In the former, 980 cubic millimeters of oxygen were consumed with no accumulation of lactic acid, while due to anærobic conditions in the latter 2.62 milligrams of lactic acid per gram of muscle were formed. This experiment would indicate that the muscle in oxygen stored approximately 2.45 milligrams of carbohydrate (its glycogen equivalent) at the expense of 980 cubic millimeters of this gas. The calculated amounts of glycogen stored, lactic acid removed, and the oxygen consumed do not agree exactly with the one to five ratio. In the case of the muscle kept under anærobic conditions, the value for lactic acid is too low while that for glycogen is too high. This muscle could not have been under strictly anærobic conditions, probably some oxygen was present dissolved in the muscle fluid and served to oxidize a portion of the acid and synthesize a small amount of glycogen. This fact is indicated by the lack of conformity between the carbohydrate loss and the lactic-acid accumulation. The underlying processes are, however, qualitatively although not quantitatively indicated. *During recovery lactic acid disappears from and glycogen is resynthesized and stored in the muscle.*

The quantitative phase of the process may be further elucidated by an analysis of the following equations which indicate the probable underlying chemical reactions.

The anærobic phase:

(1) $(C_6H_{10}O_5)n$ + $n(H_2O)$ → $n(C_6H_{12}O_6)$
Glycogen + Water → Glucose
$n \times 162$ grams + $n \times 18$ grams → $n \times 180$ grams

(2) $2C_6H_{12}O_6$ + $2H_3PO_4$ → $2C_6H_{11}O_6.H_3PO_4$ + $2H_2O$
Glucose + Phosphoric acid → Hexose-monophosphate + Water
360 grams + 196 grams → 520 grams + 36 grams

(3) $2C_6H_{11}O_6.H_3PO_4$ + $2H_2O$ → $C_6H_{10}O_6.(H_3PO_4)_2$ + $2C_3H_6O_3$ + $2H_2O$
Hexose-monophosphate + Water → Hexose-diphosphate + Lactic acid + Water
520 grams + 36 grams → 340 grams + 180 grams + 36 grams

(4) $C_6H_{10}O_6.(H_3PO_4)_2$ + $2H_2O$ → $2C_3H_6O_3$ + $2H_3PO_4$
Hexose-diphosphate + Water → Lactic acid + Phosphoric acid
340 grams + 36 grams → 180 grams + 196 grams

The aerobic phase:

(5) $C_3H_6O_3$ + $3O_2$ → $3CO_2$ + $3H_2O$
Lactic acid + Oxygen → Carbon dioxide + Water
90 grams + 3×22.4 liters → 3×22.4 liters + 54 grams

For each gram of lactic acid formed there will be $^{162}/_{180}$ or 0.9 gram of glycogen broken down. Theoretically, reactions one to four inclusive will continue until the concentration of lactic acid reaches the fatigue maximum. If, however, oxygen is simultaneously or subsequently made available the acid may never reach this concentration and the process may not run to a termination before the glycogen store is exhausted. One gram-molecule of lactic acid

or its equivalent of glucose requires 67,200 cubic centimeters of oxygen or about 747 cubic centimeters per gram for its complete oxidation. In the above experiment, 1.3 milligrams of glucose or lactic acid would require 971 cubic millimeters of oxygen for its oxidation. This figure compares favorably with that of 980 cubic millimeters calculated by Meyerhof. Since the estimated and determined values correspond so closely, it would seem obvious that the immediate substance oxidized by the isolated muscle is carbohydrate.

Resynthesis of glycogen from lactic acid.—The ratio of the carbohydrate, or its lactic-acid equivalent, oxidized to the lactic acid resynthesized to glycogen has been shown to vary considerably depending upon the nutritive condition and efficiency of the muscle. Some of Hill's experiments (3a and 3b) would indicate a ratio of one to five while Meyerhof (4) gives values as low as one to four. It will be shown in the following chapter, under the discussion of the efficiency of the recovery process, that the ratio of the oxidative to the synthetic-lactic-acid removal is usually about one to four. Assuming that this value is approximately correct, the following quantities of the reacting substances may be considered to be involved for every gram of lactic acid removed, omitting phosphoric acid from the reaction since it does not enter into the final end products:

Equivalents of intermediate and final products

$2C_3H_6O_3$ →	$C_6H_{12}O_6$ →	$(C_6H_{10}O_5)n$ +	H_2O
Lactic acid	Glucose	Glycogen	Water
1 gm. removed	1 gm.	0.9 gm.	0.1 gm.
0.2 gm. oxidized by 150 cc. oxygen	0.2 gm.	0.18 gm.	0.02 gm.
0.8 gm. synthesized to glycogen	0.8 gm.	0.72 gm.	0.08 gm.

During the resynthesis of oxidative recovery the chemical reactions are probably a reversal of those shown in reactions one to four inclusive. In order that such an endothermic series of reactions may proceed, a source of outside energy is necessary to drive them. This energy is supplied from the oxidative reaction (5) which is also responsible for the recovery heat (Chapter IV). The phosphoric acid liberated during the resynthesis process may not, in all probability, remain in the muscles as such, but may enter into the resynthesis of phosphocreatine and adenyl-phosphoric acid (page 46).

Whether lactic acid or its equivalent of glucose is oxidized does not alter the net result. Within recent years, evidence has accumulated which would seem to show that it is not lactic acid that is oxidized in recovering muscle, but its equivalent in glucose. In this case all of the lactic acid would be resynthesized to glycogen while a quantity of glucose equivalent to approximately one-fifth of the lactic acid so removed is oxidized; one part of the energy thus set free is used to drive the endothermic reactions (synthesis of glycogen); another part is lost as heat. This endothermic factor is the exact counterpart of the anærobic exothermic reaction, that is, it would not only

embody the energy necessary to synthesise the lactic acid into glycogen, but also that necessary to dissociate the acid from the buffers.

Nature of the oxidative process.—Throughout the preceding pages the reader's attention has been repeatedly called to the presence of oxidative processes occurring within the muscles whether they are in a state of rest or have previously been in activity. In an isolated muscle the onset of fatigue is determined by the net conditions prevailing at any given time in consequence of lactic-acid production and the counteracting factors, the buffering capacity of the muscle and the rate of oxidative removal. The topic of physiological oxidations will be considered in a subsequent chapter, but at this time a few general statements will help to make clear the part played by oxidation in the process of delaying fatigue and of the recovery from activity.

The rate of recovery or the delaying influence of oxidation processes during the development of fatigue is not a function of the presence of molecular oxygen in the active tissues alone, for the substances (substrates) to be oxidized, whether lactic acid or glucose, are relatively inert in the presence of molecular oxygen and are oxidised so slowly that for all practical purposes we may speak of them as not being oxidized at all. In order that oxidation of these substances may be brought about in the laboratory, *in vitro*, very high temperatures and very strong oxidizing reagents must be employed. In the animal body (body temperature) and also in surviving isolated muscles, oxidation of these substances proceeds with comparative ease and with considerable rapidity. This condition is dependent upon the presence of specific *oxidase systems* (*enzymes*) within the tissues. These catalytically accelerate, many times, the reactions which tend to occur relatively slowly in their absence.

This system of oxidation catalysts may be considered as quite definite in quantity and character for any given tissue at any given time. For chemical reactions, the velocity of the reaction may at times be determined by the quantity of catalyst present; if this is increased in amount the reaction proceeds more rapidly, if diminished, more slowly. This can only be true, however, in the presence of an excess of each of the reacting substances. If the catalyst remains unchanged in amount, it then becomes a factor which determines the velocity of the reaction. Under other conditions either of the reacting substances may become the determining factor by being added to the reacting mixture relatively slowly.

We may consider the muscle as a dynamic machine which obtains its energy from the chemical reactions which occur within it. It is even more than this for by its own activities the mechanism for energy production is aroused and regulated. It prepares its own fuel in the form of stored glycogen, it contains its own catalysts, and receives its oxygen from the blood. As will be shown in Chapter XXII, the number of capillaries and the volume of blood flowing through a muscle is greatly increased during activity. Although an attempt is made to meet the demands of activity by increasing the oxygen supply and oxidation removal of lactic acid, this is not always possible. The magnitude of the oxidative process may be determined by

various factors under various conditions. If the activity is mild, the quantity of lactic acid is so small that neither the oxygen income nor the quantity of oxidation catalysts become limiting factors and little or no lactic acid accumulates within the tissues.

From the general reactions, glycogen—lactic acid—catalysts plus oxygen, it follows that in moderate activity a point may be reached at which the various reacting substances are in such proportions as to bring about the maximum rate of oxidation. The lactic acid is no longer a limiting factor. More strenuous activity, however, produces acid in greater amounts when it is obviously not a limiting factor, but its removal is limited by either the oxygen supply or the available catalysts. The supply of oxygen is determined by the respiratory and circulatory systems while the adequacy of the catalysts is dependent upon the make-up of the tissue. Either of these may become limiting factors and thus determine the rate of recovery. The probability of the catalysts acting in this way has been little investigated, but it is not improbable that they may at times do so. Certain evidence would point to the fact that they may vary quantitatively under certain conditions from individual to individual and in various degrees of training (Chapter XXIV). Usually, however, it is the oxygen supply which is first taxed to its capacity and thus governs the rate of recovery. In isolated muscles the diffusion of oxygen is very slow and recovery, even in an atmosphere of pure oxygen, becomes very slow and requires several hours. In an atmosphere of air, recovery is never complete, lactic-acid production finally gains the ascendency and the muscle passes into rigor.

Summary

Even in the so-called state of rest, metabolic processes are constantly taking place in the cells of which the body is composed. These processes continue in surviving muscles removed from the body until cell death occurs. When the muscles are thrown into activity by means of the proper stimuli, these metabolic processes are augmented in proportion to the strength and duration of the responses. Strictly speaking, there is no time during the life of a cell, tissue or individual at which all forms of activity are suspended, neither is there a time when recovery is not in progress. The differences between the recovery process during so-called rest and so-called periods of activity are essentially quantitative only.

Irritability and, hence, response in any given tissue are temporarily suspended during the *refractory period*. As the *relative refractory phase* proceeds, the normal irritability is gradually recovered, and a period of supernormal irritability may supervene. The underlying processes of these phenomena are essentially chemical in nature.

The term *recovery* is generally reserved to designate the reinstatement of the normal resting conditions of the muscle through the removal of the waste products of the activity and the resynthesis of the normal supply of glycogen as a source of energy. The waste products are essentially lactic,

mono-phosphoric, and carbonic acids. Temporary relief of the muscles from these products is assured through the action of the muscle buffers, but permanent recovery is dependent upon the process of oxidative removal.

Recovery takes place during the interval following a simple twitch and may require several minutes for its completion. In tetanic responses, recovery begins soon after the onset of the activity and takes place simultaneously with it, the phase of recovery always lagging somewhat behind the corresponding phase of activity. At the termination of the response, several minutes are again required for complete recovery.

The following changes are known to occur in a muscle during recovery: (1) there is a gradual decrease in its lactic-acid content, (2) the glycogen content of the muscle is increased, (3) there is an increased consumption of oxygen, (4) heat is liberated in proportion to the amount of lactic acid removed, (5) the phosphorus-containing compounds, *phosphocreatine* and *adenyl-pyrophosphoric acids*, are resynthesized, and (6) the normal irritability and contractility return.

The excess oxygen consumption during recovery is only approximately twenty per cent of that which would be required to completely oxidize the lactic acid removed. For every gram of lactic acid oxidized, four are thus removed in some non-oxidative manner. This portion is resynthesized to glycogen; approximately one-half of the energy set free from the oxidation of the other fifth of the lactic acid is employed in driving the endothermic resynthesis while the other half is lost as heat.

The oxidation processes are effected through the action of the muscle oxidases. The rate of oxidation at any one time depends upon the relations which exist between the oxygen supply, muscle metabolites (substrate), and the tissue oxidases. It is probable that under the proper conditions any one of these may become the factor which determines the rate of oxidation.

QUESTIONS

1. In what ways do the metabolic processes during activity differ from those during so-called rest?
2. Define recovery of muscle and discuss whether it occurs in muscle during the so-called state of rest or only after a period of activity.
3. Define the absolute refractory and relative refractory periods.
4. Discuss the excitability of muscle before and after the relative refractory period.
5. What evidence is there that the underlying processes of excitation and recovery are chemical in nature?
6. Why are human skeletal muscles able to produce summated and tetanic contractions?
7. Why does the heart muscle of man never enter into a state of summated or tetanic contraction?
8. Discuss the discharge of nerve impulses in relation to the refractory period of muscle.
9. State the changes which occur in muscles during the development of fatigue.

10. What relationship do the aerobic changes of isolated muscle have to those of the muscle in the absence of oxygen?
11. What are the relative values of the initial heat, delayed heat, and recovery heat?
12. Discuss the evolution of the recovery heat.
13. If a fatigued muscle is deprived of oxygen, what changes will subsequently occur?
14. Upon what conditions does the rapidity of the onset of rigor depend?
15. How can you explain the fact that muscles have a period of anaerobic response?
16. What effect does an inadequate oxygen supply have on the recovery period?
17. Write a chemical equation to indicate that carbohydrate is the only food utilized by isolated muscles.
18. Discuss the ratio of oxygen consumption to lactic-acid removal.
19. What effect does the presence of oxygen during recovery have on the glycogen content of muscle?
20. Let us suppose there are fifty grams of lactic acid accumulated in the muscles. State the means by which this lactic acid is disposed of during recovery indicating the amounts converted by each method.
21. What is necessary for the recovery of muscle besides molecular oxygen?
22. What is the limiting factor to the removal of lactic acid during strenuous activity?

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TEXTBOOK OF WORK PHYSIOLOGY

PHYSIOLOGICAL BASES OF EXERCISE

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is cut until all biochemical events are stopped by freezing. The ATP-ADP recycling is extremely fast. However, a lack of ATP at a critical point in the contraction, at the myosin head, would cause rigor (Chap. 2), which is not a normal symptom of fatigue. Let us take a look at the other energy yielding phosphate compound, *phosphocreatine* (PCr). It is a potent resynthesizer of ATP but it is, to present knowledge, not directly involved in the contractile mechanisms. Its concentration falls rapidly at the onset of vigorous exercise to very low values. This could negatively interfere with the ATP level at some crucial site(s) within the cell.

A classic candidate responsible for reduced performance of skeletal muscles and fatigue is an accumulation of lactic acid. This is true when the mitochondria have inadequate access to enough oxygen, the *anaerobic processes* are recruited with an inevitable accumulation of lactic acid. As a relatively strong acid, its production should increase the proton concentration, i.e., the pH becomes reduced. There are key enzymes of importance for both the anaerobic as well as the aerobic processes that can be inhibited by a reduced pH. Whether or not critical "bottle necks" can be created is presently not known. A reduced pH could, for instance, reduce the myofibrillar ATPase activity, a key factor for efficient muscular contraction.

In Chap. 2, it was pointed out that a release of free Ca^{2+} into the cytosol was necessary for establishing a cross-bridge formation between myosin and actin filaments and therefore a necessity for muscle contraction. The trigger mechanism is the uptake of calcium on specific sites of the troponin. There is a hypothesis that another positive ion, for example H^+, could compete with Ca^{2+} and block the sites without eliciting the cross-bridge formation. There are also studies indicating that a pH decline can reduce the Ca^{2+} release from the sarcoplasmic reticulum (Nakamura and Schwartz, 1972). Therefore, at many points in the chain reaction with Ca^{2+} ions involved and leading to cross-bridge formations, protons could interfere negatively. However, no factual data are available as yet proving that this is the case. The assumption that lactate formation interferes with the contractile and biochemical process is opposed by a recent proposal, which suggests that the hydrolysis of ATP, *not* lactate production is the dominant source of the intracellular acid accompanying an anaerobic energy yield (see Busa and Nuccitelli, 1984). If, in experiments, the pH in activated muscles is kept at a given level the muscles contract with a high power even if the lactate concentration is very high. It is also an interesting observation that the highest lactate concentration in muscle and blood is usually observed in well-trained athletes participating in important competitions, not when the same athletes perform a subjectively "all-out" test in the laboratory. Apparently, muscles can function despite a higher lactate level if the athlete is particularly well motivated.

Summary The ability of the muscle fibers to maintain a high force, and the individual's subjective feeling of fatigue, depend on the blood flow through the muscle. At the beginning of exercise, there is a time lag between blood demand and blood supply. In very short spells of isometric contraction, ATP and phosphocreatine can yield energy and the oxygen present in the muscle (bound to myoglobin) also makes possible an energy delivery from aerobic processes. A maximal contraction can, however, be sustained for only a few seconds. In isometric contractions with less than 15

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Exhibit D

Fundamentals of Human Performance

1987

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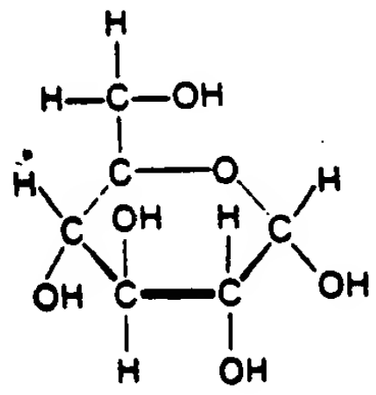

Figure 3-1
Structure of glucose, a simple sugar. Five carbons and an oxygen atom serve to create a hexagonal ring conformation. Shaded lines represent the three-dimensional platelike structure.

cells, with the possible exception of contracting muscle and heart, require insulin for glucose uptake. The central and peripheral nerve cells as well as kidney and red blood cells depend heavily on glucose as a fuel source. In fact, if blood glucose levels fall too low during exercise, brain and nerve function will be so impaired as to cause exercise to stop. Heart and skeletal muscle can use alternative fuels (mainly fatty acids), but the heart and muscle also appear to require glucose or stored glycogen for high rates of energy output.

The liver uses mainly fatty acids as its fuel source, but it can also utilize glucose. Following a carbohydrate-rich meal, the liver will take up large amounts of fats released into the circulation by the digestive system. It has recently been found, however, that most of the glucose released into the circulation from the digestive system bypasses the liver (Figure 3-2). In the peripheral musculature, glucose is taken up and stored as glycogen or released mainly as lactate, but also as pyruvate and alanine. These substances then circulate to the liver where they are converted to glucose 6-phosphate and released into the blood as glucose or stored as glycogen. Fat cells in adipose tissue also consume glucose. In adipose tissue, glucose serves to stimulate fat (triglyceride) synthesis.

Glycolysis

The metabolic pathway of glucose breakdown in mammalian cells is termed glycolysis. The process is frequently referred to as a metabolic pathway because it proceeds by a specific route, involving specific steps (intermediate products), in which each step is catalyzed and regulated by a specific enzyme.

Aerobic (Slow) and Anaerobic (Fast) Glycolysis

There are two general ways to describe glycolysis—fast and slow glycolysis. Alternatively, the terms anaerobic (for fast) and aerobic (for slow) glycolysis are used. The terms *aerobic* (meaning with air, air contains O_2), and *anaerobic* (meaning without O_2) were developed by pioneer biochemists such as Louis Pasteur.

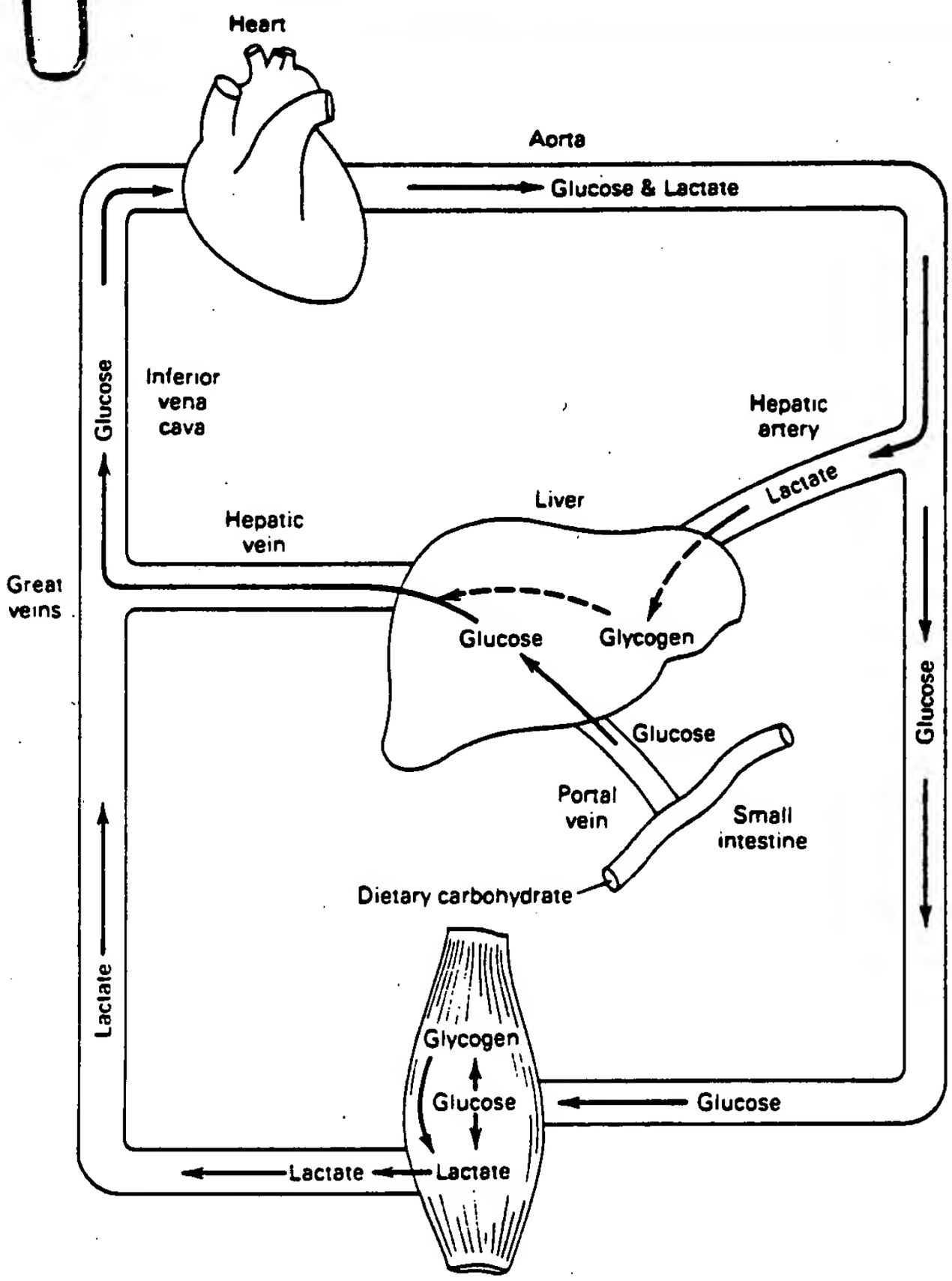

Figure 3-2
Diagram of the new glucose to hepatic glycogen pathway ("glucose paradox") by which the liver prefers to make glycogen from lactate as opposed to glucose. Glucose released into the blood from the digestion of dietary carbohydrate bypasses the liver and is taken up by skeletal muscle. The muscle can either synthesize glycogen or produce lactate. The lactate then recirculates to the liver and stimulates glucose and glycogen formation. See Foster, 1984.

$$\text{Pyruvate} + \text{Glutamate} \xrightarrow[\text{GPT}]{} \text{Alanine} + \alpha\text{-Ketoglutarate} \qquad (3\text{-}4)$$

Alanine recirculates to the liver to undergo gluconeogenesis in a process called the glucose–alanine cycle. This recycling of carbon-containing molecules is very important in maintaining blood glucose levels during starvation because the amino acid glutamate is derived largely from muscle protein stores. The glucose–alanine cycle is also thought to help maintain blood glucose levels in prolonged exercise.

During exercise approximately 20% of the glucose released from the gluconeogenic organs results from substrate recycling (i.e., the Cori and glucose–alanine cycles). Glycogenolysis in liver supplies the remaining 80% of glucose released into the circulation during prolonged exercise. Therefore, preexercise nutrition by raising muscle and liver glycogen reserves, can be very important for maintaining glucose homeostasis during exercise (Chapter 14).

The Lactate Shuttle

Recently, isotope tracer studies have allowed precise estimation of the rates of lactate and glucose production and oxidation during sustained, submaximal exercise. The results indicate that lactate is actively oxidized, and may be a preferred fuel in heart and red skeletal muscle fibers. Within a muscle tissue during sustained exercise, lactate produced at some sites, such as Type IIb (FG) fibers, diffuses or is transported into Type I (SO) fibers (Figure 3-12). Some of the lactate produced in Type IIb fibers shuttles directly to adjacent Type I fibers. Alternatively, other lactate produced in Type IIb fibers can reach Type I fibers by recirculation through the blood. Thus, by this mechanism of shuttling lactate between cells, glycogenolysis in one cell can supply a fuel for oxidation to another cell. Skeletal muscle tissue then becomes not only the major site of lactate production but also the major site of removal. In addition, much of the lactate produced in a working muscle is consumed within the same tissue and never reaches the venous blood.

Lactate–Glycogen–Glucose Interrelationships in the Body

On the basis of contemporary radiotracer studies as well as the classic studies of the Coris, a different, but more unified view of carbohydrate metabolism in the body is emerging. As suggested in Figure 3-2, dietary carbohydrate enters the blood as glucose. However, some of this glucose bypasses the liver and gets metabolized to lactate in the musculature. The lactate released from

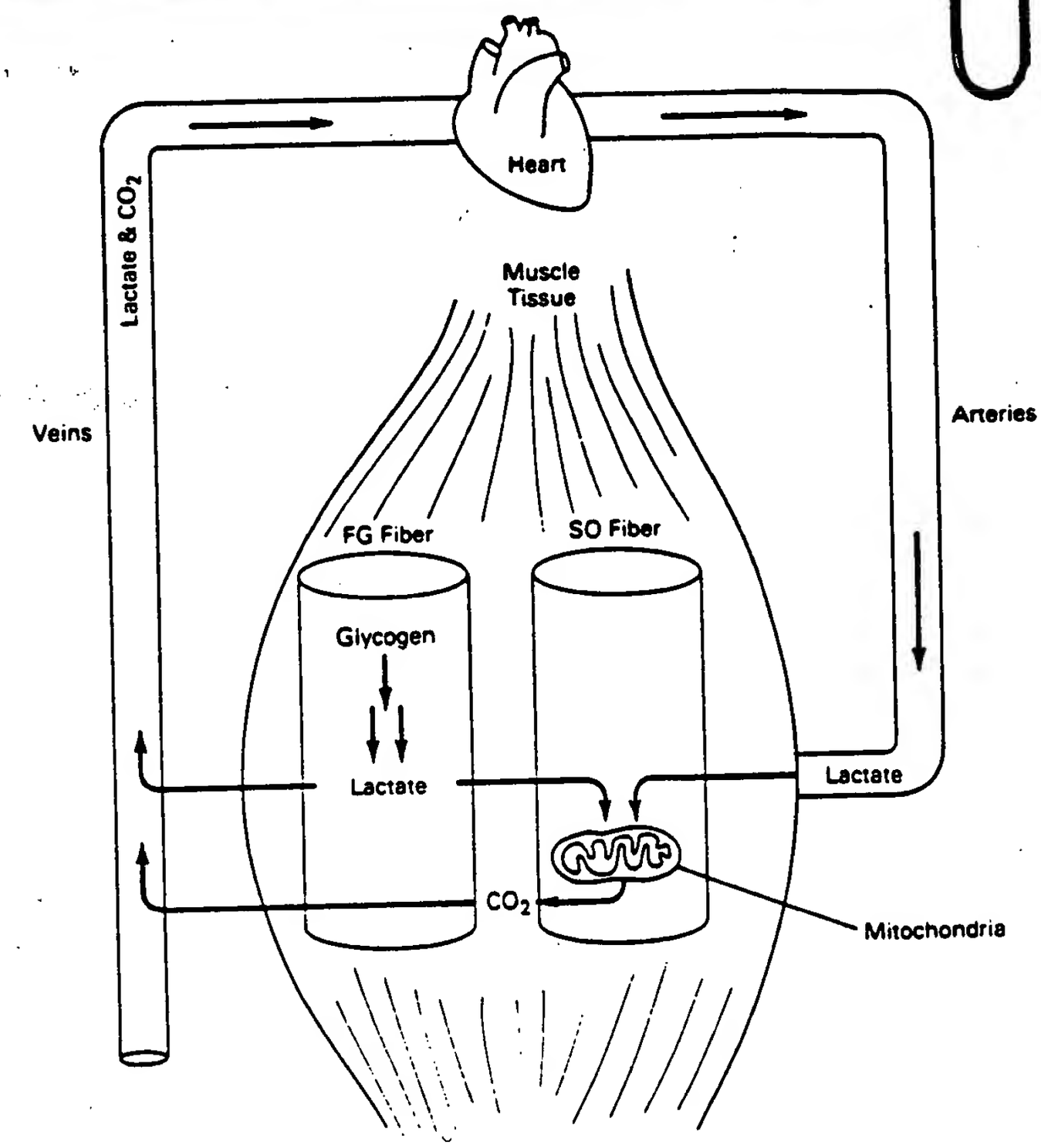

Figure 3-12
Diagram of the lactate shuttle. Lactate produced in some cells [eg., fast-glycolytic (FG, Type IIb) muscle cells] can shuttle to other cells [eg., slow-oxidative (SO, Type 1) fibers] and be oxidized. Also, lactate released into the venous blood can recirculate to the active muscle tissue bed and be oxidized. During exercise the lactate shuttle can provide significant amounts of fuel. See Brooks, 1985.

muscle recirculates to the liver, where it can stimulate glucose production and release as well as glycogen synthesis. In the contemporary literature, this process is called the "glucose paradox" (referring to the liver's preference to make glycogen from lactate rather than glucose).

During sustained exercise, a similar thing happens. Glycogenolysis in muscle, particularly FG muscle, results in the release of pyruvate, lactate, and alanine into the circulation. When these substances reach the liver, they